

American Journal of Obstetrics and Gynecology

VOL. 39

FEBRUARY, 1940

No. 2

**American Association of Obstetricians, Gynecologists and
Abdominal Surgeons**

Fifty-Second Annual Meeting, September 7, 8, and 9, 1939

PRESIDENTIAL ADDRESS*

JAMES E. KING, M.D., BUFFALO, N. Y.

I DESIRE first to express to the members of this Association my heartfelt appreciation for the honor conferred upon me in electing me President. Those of you who have occupied this chair will understand my feelings, and the younger members no doubt cherish the hope that they one day will have this experience.

In my address, I regret that I cannot bring you any new scientific truths. It would seem, however, that there is no subject which should have greater interest for this Association than a discourse on woman, herself. Not a discussion on her beauty or her diseases, for those we know, but rather to attempt to account by fact and fancy for her peculiarities and to explain her inconsistencies, and those delightful surprises we so often experience in our contacts with them.

Woman for centuries has been the slave of man. In China and India, the majority of women may still be regarded as slaves. It is only in the past one hundred years, and in those countries most highly civilized, that woman, by persistent effort, has succeeded in securing for herself the economic and political rights so long enjoyed by man. Occasionally before the nineteenth century, some lone woman's voice was heard in protest. In 1638 Anne Hutchinson was excommunicated and banished from the Massachusetts Colony because she had criticized the men in authority and had dared to preach. It was said that she had spoken "with the impudent boldness of a proud dame." Even in 1844, the Reverend Danforth reflected the views of his day when he wrote,

*Given at the Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 7 to 9, 1939.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

"Home is the palace of the husband and father. He is the monarch of that little empire, wearing a crown that is the gift of heaven, swaying a sceptre put into his hands by the Father of All, acknowledging no superior and fearing no rival." And this less than one hundred years ago! Even in the scriptures these views found support. Every woman today must regard with contempt the opinions the Apostle Paul expressed in his epistles concerning the place of woman. There was also a basic human principle involved in this position of woman. It is inherent in mankind for the stronger groups to attempt to subjugate the weaker. This is evident today in this troubled world of ours. The fact that woman is physically weaker than man, in part, accounts for man's attempt to dominate her. Moreover, this very weakness made it necessary in the past for her to look to him, the stronger, for protection. The matter of education also played its part. Only a few centuries ago, learning was reserved for men, and women were accorded a scant share in what education there was to be had. As men became wiser, it afforded them further excuse for assuming the ascendancy.

Today in all advanced civilizations, woman has succeeded in emancipating herself from the position she has occupied in the past. She is respected; she has acquired the same social, economic, and political privileges as men; she is protected by the laws and ethics of the community in which she lives; she is the equal of man in all respects except one—she is still, and always will be, the weaker physically. This physical difference will always exist, for her endocrine glands design and determine her physical characteristics. This lack of physical equality, however, today is unimportant, for physical strength is neither necessary for her protection, nor essential in her acquiring the means for her support.

But granting that all that has been said is true, and that woman has attained equality with man, we still have to recognize another great difference, a difference that may be found to lie in the mental approach of woman to the problems of life, and the reactions she exhibits in her contacts with others. Nineteen years ago, I presented a paper before this Association in an attempt to account for the physical and mental differences between man and woman. It was based upon the then meager knowledge of the endocrine system. Much said at that time was frankly admitted to be theory, but inasmuch as some of those theories have since become established facts, one may speak with more assurance upon the subject we are to discuss today.

Human beings, as well as lower animals, are still activated, and their behavior influenced, by the struggle for self-preservation and the urge to reproduce. With the ramifying interests and complexities of our civilization, often it may be difficult to recognize the influence that these fundamental laws play in our lives.

In the human family, as well as in most animals, the burden of reproduction is entirely borne by the female. From puberty through the menopause, woman is under the domination of her reproductive glands. For about thirty years of her life, conditions are reproduced each month that make possible the implantation and development of a fertilized

ovum. The secretion of her anterior pituitary causes to develop during each menstrual cycle, two temporary glands, the Graafian follicle and the corpus luteum. Should pregnancy occur, in addition to the physical changes that take place, there is a readjustment of her thyroid and pituitary, and the placenta itself, as it develops, becomes an important endocrine gland. Following the birth, another readjustment takes place, with lactation and the involution of her reproductive organs. At the age of approximately forty-five, the menopause occurs, and a marked change ensues in the physiology of her endocrine system, with frequent maladjustments that cause the discomforts from which many women suffer. The part that man plays in reproduction is simple and unattended by consequences to himself. His reproductive powers are not limited to any definite period, but they gradually wane and finally cease at an age that varies in different individuals. But for thirty years the potent chemicals secreted by her reproductive glands hold woman under constant control.

There are a number of well-recognized facts known today concerning the endocrine glands that have a bearing on this discussion. The first is that among these glands there exists a definite interdependence, and upon the normal function of each depends the normal function of one or more of the others; second, the evidence of this relationship may be seen as an inhibition, a stimulation, or as a control of normal secretion; third, that certain of the glands have a definite individual span of life, at the end of which their function ceases, a function which may extend from a few days to a few years; fourth, that the secretions consist of extremely potent chemicals and minute quantities of these enter the blood stream and are thus carried to the other ductless glands; fifth, that various glands may secrete a substance similar in its effect to that of certain of the others; and sixth, that these glands are subject to hyperplasia of the secreting cells, which is reflected in a hyperfunction, or if an atrophy of the secretory cells occurs, a hypofunction results.

It is generally conceded that physical characteristics are dependent upon the normal secretion of the endocrine system. It is also true that many of our mental characteristics depend upon the secretion of these glands, and the dominance of certain glands in an individual will determine the outstanding features of his personality. Heredity is, therefore, believed to play a part in the development of the endocrine system, and at times it appears as though this were true.

It is not difficult to believe that the potent chemicals, thrown into the blood stream by the glands, may react to develop our mental states and to influence our thought and action. That chemicals in the blood will determine thought and action is apparent in the effects produced by cocaine, morphine, alcohol, and cannabis indica.

We find sex attraction in the human family variously modified by custom and the influences which are the result of intelligence and education. Through intelligence man is able to evaluate qualities of mind in another, and this spiritual attraction, combined in varying degrees with sex attraction, constitutes the emotion called "love." Reduced

to its simplest terms, love may be regarded as the intellectual refinement of the impulses springing from gonadal secretion. Prompted by their gonads, Leanders have performed deeds of valor and faced the greatest perils. Their secretion has inspired the most noble acts as well as instigated the most sordid crimes. Surely here we cannot question the influence of the ductless glands upon mental attitudes and behavior.

In our civilization when a girl reaches the age of fourteen years, it is a time when those interested watch her with care, marveling at the physical changes that so rapidly take place, and at the still more astounding changes that occur in her mental reactions. The girl herself notes with wonder the enlargement of her breasts, the filling out of her body and other more or less definite changes that characterize her approach to womanhood. The fear or surprise that her first menstruation may cause depends upon how well she has been prepared to expect it. From this moment it would appear that she, like Mother Eve, had eaten of the fruit of the Tree of Knowledge and had thereby become sex conscious. There is developed in her that attribute, enhanced by Victorian influence, which we term modesty. She lays aside her childish views and begins to think and act as a woman. These manifestations may be observed by all, but the physician can visualize the changes that are taking place in her reproductive organs, and the complex readjustment of her glandular system necessary to bring them about. Thirty years ago, these evidences of puberty were believed to be due simply to an awakened activity of the gonads. It is now known that they occur through the interrelated action of various glands. The part played by some can as yet be explained only by theory. The thymus body, the so-called childhood gland, is one of these. Until puberty is well established, it is large, but following the first changes of puberty, it rapidly atrophies. The theoretical interpretation for this is that, its life span being fourteen years, it exerts during that time an inhibitory action upon the gonadotropic principles of the anterior pituitary. With the atrophy of the thymus, the pituitary is freed to establish the menstrual cycle. The pineal gland is also regarded as a gland of childhood, but little is as yet known of it except what is suggested by the occasional tumor which inaugurates a precocious sex development in the male.

With the complex physical phenomena that result from the secretion of the temporary glands with that of the permanent glands concerned in menstruation, it is not surprising that there also may be associated certain mental reactions during the menstrual cycle. Women so frequently experience a mental depression at those times, that slight degrees may be regarded as normal. The thyroid plays an important role in menstruation. It is observed occasionally to become temporarily enlarged. This may result in an effort of the thyroid to supply additional secretion demanded at menstruation. If the threshold can be raised to meet those requirements, no mental depression occurs. All degrees of this depression may be encountered. In some women the depression experienced may constitute a real dread of menstruation. Krugenstein has stated that in 107 instances of suicide observed by him in women in the reproductive age, all were menstruating at the time.

Other types of mental disturbance may also be seen. One that is relatively common is varying degrees of unreasonableness. Some women become unreasonable to a point where every remark and act is construed in a manner to awaken self-pity and a sense of injustice. At times even physical violence is attempted. Women who may be lovable and sweet-tempered at other times, during menstruation become termites. Entire households may look forward to the approaching period with as great dread as the women themselves. Another not uncommon manifestation is expressed in the impulse to work. Women so affected become restless, quick-tempered, and exacting in their requirements of others. They, themselves, will work at tasks which at other times they would scorn to do, or they may be possessed by a frenzy to rearrange their household effects. The slightest criticism will produce a flood of angry tears. These latter manifestations may be regarded as due to the drive and urge of an adrenal imbalance. Just how this maladjustment is brought about is not as yet understood. That it is due to a hyperadrenalism, there is scarcely a doubt. Havelock Ellis states that Lombroso found that of eighty women arrested for opposition to the police or for assault upon others, all but nine were menstruating at the time. There is more than a suspicion that adrenal dysfunction accounts also for these physical outbursts.

There are many mental reactions in connection with pregnancy that are extremely interesting, but because of our familiarity with them, they are accepted without thought as to their cause and significance. In connection with the reactions to pregnancy, however, one must be ever mindful of the modifications that may be the result of custom, necessity and economic condition of the individual or group. It is in animals only that uninhibited reactions are seen, except in women whose status and environment are such that a placid frame of mind renders possible an unstrained response to their condition.

Women frequently express a desire for children. This is due to a natural affection for the young, that is frequently shared by the husband. This is not contingent, therefore, upon an endocrine influence, but upon a memory that possibly recalls the happiness of early motherhood and a mentality that makes it possible to hope that this experience may be repeated. In women, a welcomed pregnancy brings happiness, while one that for various reasons may not be desired will bring great unhappiness.

There is no reason to believe that in animals during gestation there is any mental response. Directly following the birth, however, mother love appears. Nineteen years ago, I suggested that this developed as a result of an internal secretion and expressed the belief that it sprang from the pituitary gland. This has recently been proved to be so, and the lactogenic hormone of the pituitary has been found to cause the expression of mother love. If other evidence is necessary, there is the fact that in animals, as lactation ceases, the protective care devoted to the young will also cease. In all animals and in women during pregnancy, the so-called "pregnancy cells" of the pituitary develop. Impaired vision and headache may sometimes result from the pressure

of the enlarged pituitary. It is possible that these pregnancy cells are the specific cells that secrete this hormone. With the development of the mother instinct in animals, there may be observed changes affecting their disposition. In their unreasoning desire to protect their young, even domesticated animals may become ugly, clawing, or snapping at any who attempt to handle them or their newborn. This cannot be the result of even the most rudimentary mental process. These protective reactions are in some manner connected with the adrenals. The law of self-preservation is obviously dependent largely upon the adrenals, in both the need for unusual strength often required and a fierceness that may be displayed when necessary. It would seem possible that these glands by their secretion arouse the protective fierceness observed in these mothers.

As to the liberation of the lactogen which stimulates lactation and mother love, there is yet no definite laboratory proof. It is known, however, that the progesterone of the corpus luteum early stimulates the development of the mammary glands, and as the placenta develops, the progesterone it produces carries on the work of the atrophying corpus luteum. This placental hormone apparently not only inhibits lactation, but also holds in check the posterior pituitary. The onset of labor can reasonably be assumed to take place when the life of the placenta is brought to its close at the end of nine months. The pituitary secretion is then liberated and enters the circulation to produce contractions of a possibly sensitized uterine muscle. This is as yet pure theory, but there are the most convincing reasons for believing that the life of every placenta is definitely fixed in the various species, its span varying from twenty days in the mouse to twenty months in the elephant.

If further proof is required as to the life of the placenta, it can be found in abdominal pregnancies that go to term. At the end of nine months, the so-called spurious labor occurs. Following this the uterine contractions cease. The fetal heart sounds are no longer heard. The child is dead.

The cause of eclampsia is not known. Some day probably it will be found to be due to a dysfunction of a placenta whose perverted secretion becomes a potent poison that damages kidneys and liver, and thus, either primarily or secondarily, causes the convulsions.

It is a rather curious fact that up to about five years ago, the placenta as a ductless gland was generally neglected. This may possibly be explained by the fact that as yet no definite cells have been found which indicate that they are secretory. From the experiments of a number of investigators, however, it is now believed that progesterone is a definite placental secretion, and there is suggestive evidence that an estrogenic substance is also formed. The Langhans' cells may possibly be responsible for these secretions. It is certain that, as yet, there is nothing known of them.

In the protective care shown by birds and domestic fowl, a placenta and lactation obviously play no part. There is, nevertheless, good reason to believe that the pituitary assumes a major role, for it is

known that this gland does show definite changes during the brooding season. The hen becomes possessed by a desire to set. This desire is not prompted through a mental process, but results from the secretion of the pituitary that compels her to react in this manner. It is well recognized how difficult it is to change her purpose, and many are the rough and ready methods employed to discourage her. She will set upon anything that will pass as an excuse for an egg, and at times she will even dispense with an excuse. If, however, she does set on eggs that in due time hatch, she at once assumes a proud and protective attitude in caring for her chicks that is in every way comparable to the mother love shown by animals. The hen is a timorous bird, but in the face of a danger threatening her brood, she will display great courage in their defense. Indeed, in the protection of her chicks, she is possessed of a far greater courage than she would show at any other time, when, if a similar danger threatened her life, she would flee. The most ardent admirer of the hen would not consider her intelligent. This protective care and courage must be regarded as due to a mechanistic reaction produced by the chemicals secreted by her endocrine glands.

A mental state in women that is more or less comparable to the absorbing desire of the hen to set, is seen occasionally in those who become possessed of a belief that they are pregnant. Any woman may believe she is pregnant, but the assurance of her physician to the contrary is sufficient to convince her that she is not. There are some women, however, who may present evidence of Froelich's syndrome and in whom the belief that they are pregnant becomes an obsession. These women have infrequent menstrual flow or amenorrhea, and they will rehearse their symptoms to indicate pregnancy and evince implicit faith in them. No opinion of their physician or specialist will dispel that belief. Nothing will persuade them that they are not pregnant. They proceed with their preparation; the nurse is engaged, and in one instance the woman had convinced her physician. At the expected time of labor, the nurse and physician were summoned, and her conviction was shattered only by the fact that no baby was forthcoming. With the other evidences of pituitary dysfunction in such women, it is perfectly possible that this unreasoning belief in pregnancy is due to pituitary dysfunction.

During the menopause almost all nervous disturbances or other manifestations that may occur are attributed by the laity, often quite correctly, to "the change of life." Personally, I like that phrase "the change of life," as it expresses in simple English and so perfectly what has taken place. For the physician it signifies that the ovaries have run their span of life and their function has been brought to a close. For many years the phenomena observed during this time were attributed to simple withdrawal of ovarian secretion. Today, while withdrawal of ovarian secretion is still recognized as the underlying cause, the manifestations are now known to be the result of maladjustment of other glands. The clinical evidences of the menopause are well known but the glands that produce them still offer a wide field for

study. However, two glands, the thyroid and adrenals, stand out prominently. The various degrees of depression and the usual increase in weight observed at the menopause are often associated with the lesser states of hypothyroidism. The hot flushes and other indications of a disturbed sympathetic nervous system present good reasons for associating them with the adrenals. Whether these phenomena are due to uncontrolled sympathetic nerves that affect at random the vasomotor system, or whether the sympathetics act directly upon the adrenals to produce them is not known. The fact that all these symptoms can be relieved by administering the estrogenic hormone indicates beyond question that the cause is its abrupt withdrawal.

Woman is definitely a reproductive machine. What she has accomplished against great odds in raising herself from slavery to her present position, must inspire in all the greatest admiration. She has brought this about despite the many and frequent readjustments of her endocrine secretions, and the effects they produce in her mental reactions and behavior.

Woman also has acquired prominence in science and in purely intellectual pursuits; again in spite of her active glandular system. While for these achievements we admire and respect her, we love her for herself alone. It is man's conceit that prompts him at times to feel a supremacy. It is woman who actuates man to the accomplishment of his noblest ambitions. She is the inspiration for all his great and good achievements. He labors for her; he serves her; he is her slave. He is enthralled by the sublime heights to which her virtues may raise her and at times sorely shocked at the iniquitous depths to which she may sink. She has been the enigma of all ages, a creature swayed by moods and impulses. Neither the imagination of the poet nor the wisdom of the philosopher has solved her. But the solution is now at hand; it lies in those complex and potent chemicals, the secretions of her endocrine glands.

As one contemplates the changes which have taken place in woman's estate in the past one hundred years, and considers the economic importance which today she often assumes in supporting a husband and home, one may well wonder what her position will be in the next one hundred years. Will she, as some timid souls fear, mentally and physically dominate and enslave us as we in the past enslaved her? Probably not; so long as she is controlled by her reproductive glands, she will remain basically the same loveable and gracious homemaker. Yet one is occasionally half persuaded to agree with Tom Moore for:

"Disguise our bondage as we will,
'Tis woman, woman rules us still."

THE PHYSIOLOGY OF THE ANTERIOR PITUITARY AND A NOTE ON THE MEDULLOTROPHIC HORMONE*

J. B. COLLIP, MONTREAL, CANADA

(From the Department of Biochemistry, McGill University)

I HAVE chosen as the subject for this oration, "the physiology of the anterior pituitary." The subject itself is so large that it will be quite impossible, in the course of one short address, to do more than scant justice to it. Van Dyke,¹ in 1936, published an excellent critical review on the physiology and pharmacology of the pituitary. This was based upon some 5,000 original articles touching upon this subject and this year this same author published a companion volume² on the same topic in order to bring his review of the current literature up to date. As these most excellent reviews of Van Dyke, as well as those of others,³ are readily available, and also due to the hopeless nature of the task of adequately reviewing the literature in one lecture, I have decided that I can do best by discussing for the most part certain points in which I have special interest and which I hope may be of interest to you.

As a result of the pioneer work of such men as Horsley, Cushing, Aschner, Evans, Smith, Riddle and others, great advances have been made in our knowledge during recent years of the functions of the pituitary gland. There still remains, however, much investigational work to be done before we have a complete picture of the full significance and properties of this particularly wonderful gland. The great acceleration in the pace at which new information has been obtained relative to anterior pituitary functions has in a large measure been due to the greatly increased availability to laboratory workers of hypophysectomized animals, and here the work of P. E. Smith, Van Dyke, and Selye has been of great value.

Many individual laboratories throughout the world have each contributed to the development and unfolding of the many intricate problems relating to the physiology of the anterior lobe, and perhaps, in this, there has been no better illustration in the prosecution of scientific studies of the value of teamwork than has been seen here. This teamwork has been evidenced not only in individual laboratories but between different laboratories, both of the same institution and also of other institutions, and one might add that this cooperative effort has known no international boundaries.

One of the most perplexing problems confronting almost all workers in this field has been the multitudinous number of clear-cut physiologic effects of carefully prepared anterior lobe extracts. Since the number of cell types in the pituitary is definitely limited, even though

*Joseph Price Oration, delivered at the Fifty-Second Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, at Hot Springs, Va., September 11 to 15, 1939, and revised for publication December, 1939.

the three lobes be included, it is obvious that the number of true pituitary hormones must be very limited. This being the case, it follows that each true hormone most likely has several different physiologic effects. The following list represents some of the more important physiologic effects of anterior lobe extracts which are well authenticated: (1) Specific stimulation of general body growth. (2) A thyreotropic action. (3) A gonadotrophic action. (4) A corticotrophic action. (5) A mammary secretagogue action, or prolactin effect. (6) A diabetogenic effect. (7) A ketogenic effect. (8) An increase in liver fat. (9) A lowering of respiratory quotient. (10) Change in blood lipoids. (11) Increasing oxygen consumption in thyroidectomized animals. (12) Inhibition of insulin hypoglycemia. (13) Inhibition of adrenalin hyperglycemia. (14) Retention and increase of carbohydrate stores; glycotrophic or glyceostatic effect. (15) Chromatophore- and erythrocyte-expanding effects.

While there is this formidable array of proved physiologic effects of anterior lobe extracts, one must agree with Carlson⁴ who recently stated: "Many of the pituitary gland products, fractionated by modern biochemical methods and demonstrated to have physiologic and pharmacologic actions, have not as yet been shown to be true pituitary hormones—that is, to be secreted into the body fluids by this gland in health or disease." With further reference to pituitary extracts in the clinical field, Carlson added: "The least encouraging situation today is the clinical application of laboratory findings in the pituitary field. These findings have improved our diagnosis of pituitary diseases in man, but have added little to their control. At least we have not scored a success in pituitary therapy comparable to that in thyroid, pancreas and parathyroid disorders." These remarks of Carlson were made in 1936 but in general they are equally pertinent today. I realize that I am addressing an audience essentially of clinicians and if at the outset I appear to adopt a note of pessimism as regards the practical clinical application of laboratory findings in anterior lobe physiology, I do not wish by so doing to have you infer that I think that the situation is hopeless. I have, in fact, great confidence that many things of great practical value will ultimately emerge when we know more about the basic nature of pituitary disease in the human subject.

Although information of the greatest value has been obtained by the so-called chemical dissection of anterior lobe tissue into different fractions, each with its own physiologic and pharmacologic properties, it must be remembered always that the intact normal gland is functioning as a whole in the closest relationship and coordination with the nervous system and numerous other glands of the endocrine chain. This being the case, is it any wonder that the practical application of the known facts of anterior pituitary physiology has been very slow in its development?

As a result of a considerable experience, extending now over some years, in the preparation and testing of various anterior lobe extracts and of determining the effects upon extracts and their physiologic

properties of varying physical and chemical procedures, I have come to the conclusion, like some others, that the number of true anterior lobe hormones must be very small, and thus in keeping with the anatomic nature of the factory which produces them. It is my opinion, for the moment at least, that all of the physiologic activities of the anterior lobe are represented by different groupings in two or three protein substances secreted by the gland. Granted that each specific effect of anterior lobe extracts is due to a specific group in a protein molecule, which molecule also contains other physiologically active groups, it would be possible to visualize the act of secretion of the normal gland in situ in one of two ways. Either the individual physiologically active groups may be liberated by some hydrolytic process, probably enzymatic, from the native protein carrier, or else the secretion consists of native proteins, each carrying many active groups. For example, in the former case one could visualize relatively small molecules representing the corticotrophic substance being set free in the circulation and being picked up and acting upon the cells of the adrenal cortex; in the latter case one would infer that different peripheral structures are acted upon by different groups in the hormone molecule, a specific group having always a specific physiologic effect.

As more is learned in the future about the basic facts of the normal secretory activity of the anterior lobe and of the manner in which this may be influenced by specific changes in the environment, external or internal, the nearer will approach the time of more rational therapeutic control of pituitary disease. Already, through the study of the effects of the products, both natural and synthetic, of other glands upon anterior lobe function and structure, very valuable therapeutic leads seem to be emerging. But here, as elsewhere in the endocrine field, the question of species variation must be considered. No matter how clear-cut the effects of certain hormone treatment of certain animals may be, there can be no certainty that the human individual will show the same response until an experimental study along similar lines on the human subject has given a positive answer. I have often wondered whether clinicians as a whole realize that in introducing any hormone preparation into the human subject they may be influencing not only the specific function for which the particular hormone is given but in general perhaps several endocrine glands other than the one which is presumably hypofunctional and on account of which the specific treatment has been administered. The results of such influence of an administered hormone upon the endocrine system in general may, it is true, be very desirable, but on the other hand this may not be the case. I have raised this point for the sole purpose of re-emphasizing the fact that the endocrine system acts as a whole and that disease of any one gland can each equally well produce repercussions in any part or all of the remainder of the endocrine system. Since the pituitary is now well established as the master endocrine gland, recognition of this general principle should always be uppermost in the mind of the clinician when called upon to treat pituitary disease by therapeutic measures.

CERTAIN ANTERIOR LOBE PRINCIPLES OBTAINABLE IN EXTRACTS

The Growth Hormone.—General Considerations: The term growth or somatotrophic hormone refers to that phase of anterior lobe activity having to do with growth in the sense of increasing size rather than the differentiation of bodily tissue in general. The term is somewhat a misnomer since other phases of anterior lobe activity also have to do with growth. Thus each of the gonadotrophic, thyrotrophic and corticotrophic substances has a specific growth effect upon the respective target organ. It must be assumed that this hormone, as well as other pituitary hormones, is not absolutely essential to life since completely hypophysectomized animals may live for many months; but growth, except in the case of the animal hypophysectomized while still immature, does not take place.⁵ Although no increase in bodily size occurs in the untreated hypophysectomized animal, there is plenty of evidence that the cells of individual organs can multiply and be replaced by new ones. Compensatory hypertrophy of the remaining kidney occurs after unilateral nephrectomy. The proliferation of fibroblasts and epithelial cells in wound healing is not seriously interfered with by hypophysectomy.⁶ Numerous mitotic figures have been seen in the mammary gland of hypophysectomized pregnant rats at the time of parturition.⁷ Transplanted tumors grow in hypophysectomized rats, though less rapidly than in normals.⁸ Growth of various organs may therefore be largely independent of the pituitary growth hormone and the function of the latter would seem to be the regulation of the increase in the size of the body as a whole with a harmonious and proportional increase in the size of all the organs.

Since no absolutely pure growth hormone either in the chemical or the physiologic sense has been obtained, it is difficult to decide just what physiologic effects are related to this substance and not to any other. One of the difficulties here is the great variation in the threshold dose of the different anterior lobe principles. Thus the threshold for growth in the hypophysectomized rat is extremely low. A purified growth extract may cause growth when administered daily in as small an individual dose as $\frac{1}{500}$ c.c. of an extract, 1 c.c. of which represents 1 gm. of fresh anterior pituitary substance. Such animals show no evidence of stimulation of the thyroid, suprarenals, or gonads. A much larger dose, however, may result in repair of the cortex of the suprarenal but yet have no effect upon the thyroid or gonad. The same extract, tested in adequate dosage upon the pigeon, usually shows a definite prolactin effect. Unless these important differences in the threshold dose for different physiologic responses are taken into account, one is likely to be led astray as regards the purity of any one extract.

A great deal of emphasis can be placed upon the fact that the ratio between certain different types of physiologic activity may be made to vary considerably by varying the method of extraction and processing of extracts, and thus a basis for argument can be had that each of these effects is due to a separate hormone.⁹

The Functions of the Growth Hormone.—The general control of orderly bodily growth is probably the chief function of the growth principle. The profound effect upon skeletal structures, particularly the cranium, of hypophysectomy and the correction of such by extracts of anterior lobe rich in the growth hormone illustrate in a very striking manner the physiologic significance of growth hormone activity. While it probably has little effect upon differentiation of the soft tissues, the recent work of Mortimer¹⁰ suggests that this principle has to do with skeletal growth and differentiation in a manner somewhat different from its effect on muscle, for example. Mortimer showed quite clearly that the skull of the hypophysectomized young rat failed to differentiate even though some increase in size did occur. He has summarized the effects of hypophysectomy on the cranium of the rat as follows:

"A marked decrease in vascularity of bone, affecting individual bones in proportion to the abundance of their normal vascular supply, and to the degree and pattern of differentiation that they normally are called upon to undergo in growth.

"The processes of *pari passu* resorption and deposition are seriously disturbed, the former apparently being more affected than the latter.

"All growth does not cease: cranial height and width reach materially normal dimensions; antero-posterior growth suffers.

"The snout is more affected than the brain-case; growth is inadequate in all directions.

"A roentgenologic diagnosis of completeness of the operation can be rapidly and reliably arrived at from the following observations: the cranium is small for the age and sex of the animal; the snout is disproportionately small relative to the brain-case. The calvarial outline corresponds, *in form*, to about the age at which the animal was hypophysectomized, although the dimensions may have increased. The middle table in the calvaria is hypoplastic, and in consequence presents the appearance of being obliterated, especially in the parietal bone. The frontal sinus-homologue is hypoplastic. The characteristic tooth changes described by Schour and Van Dyke are seen."

Mortimer was able to show that these defects could be corrected to a large degree by treatment with the growth hormone (Q fraction).¹¹ This fraction seemed to have a specific effect upon the vascularity of bone, restoring the normal architectural structure of the diploe, the frontal sinus homologue, and cancellous bone throughout the cranium. There resulted a satisfactory growth and differentiation in the snout, and the incisor teeth showed a normal x-ray appearance in the part grown after treatment was started.

The favorable effects of treatment of hypophysectomized animals with certain anterior lobe growth extracts upon protein metabolism¹² and upon calcium balance are due most likely to the action of the growth hormone.¹³

The growth hormone has a specific chondrotrophic action. This fact has been established by the work of Silberberg¹⁴ and more recently by that of Freud, Levie and Kroon.¹⁵ These latter authors, who have published a most valuable contribution to this phase of the subject, have summarized their findings as follows: "After hypophysectomy, longitudinal bone growth ceases, especially in the tail, and seven days after operation the difference between operated and control animals may be readily detected in skiagrams. The epiphyses are closed soon after hypophysectomy. Epiphyseal closure, once completed, cannot be reversed by treatment with growth hormone. Growth hormone treatment, when commenced immediately after hypophysectomy, prevents epiphyseal closure and maintains normal longitudinal growth in the tail. The assay of growth hormone is simple and reliable, using as indicator the tail length and vertebral development as shown by serial skiagrams. A minimal requirement of 6 mm. growth is advised as a basis of comparison between unknown and reference standard preparations. The growth defect after hypophysectomy is definitely localized in the growing epiphyseal cartilage. The histologic features of the process of growth cessation after hypophysectomy are exactly analogous to those exhibited at the end of the normal growth period. Hypophysectomized rats show no alteration in the development of bone tissue, and desmal bone, such as cranial bone, develops normally. Growth hormone has a biologically typical point of attack at the proliferating cartilage and the terms growth hormone and chondrotrophic hormone are therefore synonymous."

If the new method of assay of the growth principle developed by Freud and others proves as satisfactory in the hands of others as it has in theirs, it will represent a great advance in the matter of standardizing preparations for clinical use.

The Thyrotrophic Hormone.—The interrelationship between the pituitary and the thyroid was first suggested by Rogowitsch¹⁶ who noted enlargement of the pituitary of dogs and rabbits following thyroidectomy. Adler¹⁷ discovered that cauterization of the hypophyseal anlage in larval amphibia prolonged the larval state. Coincident with this, Gudernatsch¹⁸ found that precocious metamorphosis was induced in tadpoles by thyroid feeding. Allen,¹⁹ using the Adler technique for removal of the pituitary, showed that the delayed metamorphosis of hypophysectomized tadpoles was associated with scanty deposition of colloid in the thyroid. The Smiths²⁰ reported that the thyroid of hypophysectomized tadpoles became extremely atrophic and that repair of the thyroid could be brought about by homotransplants of pituitary or by intraperitoneal injections of extracts of bovine anterior pituitary. Spaul²¹ produced hypertrophy of the thyroid and acceleration of metamorphosis by injections of anterior pituitary substance. Uhlenhuth and Schwartzbach²² showed that salamander larvae injected with anterior pituitary extracts consumed 40 per cent more oxygen than normal larvae. The classic work of P. E. Smith²³ on hypophysectomy of the rat established quite conclusively that the thyroid is dependent on the stimulating action of the pituitary; associated with the atrophy of the thyroid of the hypophysectomized rat, Foster and Smith²⁴ found that the metabolic rate was decreased as much as 35 per cent.

A close relationship between the pituitary and the thyroid has been demonstrated clinically. Cushing²⁵ stated that patients with hypopituitary conditions tend to have a subnormal metabolism. Loeb and Bassett²⁶ and Aron²⁷ produced hyperplasia of the thyroid of the guinea pig. Numerous workers have reported on the production of hyperplasia of the thyroid in a variety of laboratory animals: Janssen and Loeser,²⁸ Watrin and Florentin,²⁹ Grab,³⁰ and Junkmann and Schoeller³¹ in the guinea pig; Benedict, Putnam and Teel,³² Houssay, Biasotti and Magdalena,³³ and Schittenhelm and Eisler³⁴ in the dog; Baumann and Marine³⁵ in the rabbit; Riddle and Polhemus³⁶ in the pigeon; Noether³⁷ in the hen; Schockaert³⁸ in the duck; and Anderson and Collip³⁹ in the rat.

Hyperplasia of the thyroid of the guinea pig has been demonstrated in vitro with the thyrotrophic hormone by Eitel, Krebs and Loeser,⁴⁰ while Houssay, Biasotti and Magdalena³³ and Marine and Rosen⁴¹ produced hyperplasia in homotransplants and autotransplants of thyroid tissue in animals injected with anterior lobe extracts.

The administration of adequate amounts of the thyrotrophic hormone to normal animals results in the course of a few days in enlargement and hyperplasia of the thyroid. There is an increase in the metabolic rate (Siebert and Smith,⁴² Verzar and Wahl⁴³), increase in the heart rate (Schittenhelm and Eisler⁴⁴), exophthalmos (Schockaert,³⁸ Loeb and Friedman⁴⁵), a reduction of the iodine content of the gland (Loeser,⁴⁶ Schockaert and Foster⁴⁷), and an increase in the alcohol-insoluble iodine of the blood (Closs, Loeb and MacKay,⁴⁸ Grab,⁴⁹ Schittenhelm and Eisler⁴⁴).

The increase in metabolism resulting from treatment of normal animals with the thyrotrophic hormone is not large as a rule. Anderson and Collip⁵⁰ reported an average increase of 26 per cent in a large group, whereas in goitrous rats similarly treated, increases in metabolic rate as high as 162 per cent of normal were seen. These animals showed marked signs of hyperthyroidism, irritability, weakness, exophthalmos, and excessive sweating.

Hypophysectomized rats show a decline in metabolic rate to an average value about 74 per cent of normal. The thyroid glands decrease in size and the cellular elements show marked involution. The metabolic rate, the size and structure of the thyroid of these animals can be restored to normal by adequate treatment with thyrotrophic extracts.

The anterior lobe appears to have a two-fold action upon the thyroid: one to influence the rate of discharge of secretion, the other to change the morphologic structure of the gland. It is doubtful, as assay studies show, whether the mechanism involved in each case is the same.

It is possible that the thyrotrophic substance has effects other than those upon the thyroid gland. Marine and Rosen⁴¹ have produced exophthalmos in thyroid-

ectomized guinea pigs. This they attributed to stimulation of midbrain centers by some constituent of the extract used. Gaebler⁵¹ has shown that the basal metabolism of thyroidectomized dogs can be raised by anterior lobe extracts containing thyrotrophic hormone. Recent work in my laboratory⁵² has shown quite conclusively that the factor responsible for the increase in metabolism in the thyroidectomized animal is not the thyroid-stimulating hormone, but a specific hormone substance probably produced in the pars intermedia. In this same connection, mention should be made of the work of Riddle and others⁵³ who showed that their prolactin preparation raised the basal metabolic rate in the thyroidectomized pigeon.

The Gonadotrophic Hormone(s), or Maturity Factor(s).—The demonstration by Smith and Engle⁵⁴ and by Zondek and Aschheim⁵⁵ of the gonadotrophic effects of implantations of anterior lobe tissue formed the basis for all the work of recent years which has established that the anterior lobe, by virtue of its hormone influence and control of the gonads, is of paramount importance in all phases of sex physiology. There are two main types of physiologic effect of gonadotrophic preparations of anterior lobe tissue upon the ovary: (1) maturation of immature follicles and (2) luteinization. Evidence obtained from work with extracts points to the mediation of these two effects by two separate and distinct substances. There is also indirect evidence that the intact pituitary may under certain circumstances produce more or less of either of these two substances. The problem is complicated further by the fact that extracts of human placenta, pregnancy blood, and urine contain a gonadotrophic substance which is not identical with the anterior lobe gonadotrophic substance. Also, pregnant mare's serum contains a gonadotrophic substance which is comparable in its physiologic effects with true anterior lobe gonadotrophic hormone and not with human placental gonadotrophic hormone. Space will not allow of a discussion of the interesting and fascinating experimental work which has been done with each of these three gonadotrophic substances. The reader is referred, accordingly, to the very excellent monographs of H. B. Van Dyke.^{1, 2}

A point of great practical interest is the close association in extracts of the anterior lobe of the thyrotrophic and gonadotrophic substances. There is a considerable variation among different species of the thyrotrophic and gonadotrophic potency of the anterior lobe. This fact can be turned to practical use in the preparation of extracts. Thus the anterior lobes of cattle have a relatively low content of gonadotrophic substance and a relatively high content of thyrotrophic hormone; the anterior lobes of sheep present the reverse condition, while those of pigs have a high content of each of these factors.

There is now experimental evidence to show that the discharge of gonadotrophic hormone from the intact pituitary of the postpubertal human female is rhythmic. This hormone may be detected in the urine, and quantitative methods are available for its estimation. Recently Venning, Henry, and Browne⁵⁶ have introduced a quantitative method for the estimation of pregnandiol in the urine. Since pregnandiol appears to be an index of luteal hormone metabolism, this allows of an indirect but probably fairly accurate determination of the duration and amount of luteal activity. It is therefore possible to estimate the functional activity of the anterior lobe as regards its ovary-stimulating action and to determine fairly accurately, as Venning and Browne have done, the time of ovulation and the duration of the luteal phase in individual cases. It would be difficult to overestimate the importance of the development of quantitative methods such as these and others to the clinical study of problem cases of disturbed pituitary or ovarian function, of abortion and of the toxemias of pregnancy.

The Corticotrophic Hormone.—Smith⁵⁷ showed that marked atrophy of the adrenal cortex took place following hypophysectomy in rats and that this degenerative change could be prevented or the normal condition restored by intramuscular implantations of fresh rat pituitaries. Collip, Anderson and Thomson⁵⁸ showed that the restoration of the atrophic cortex of the hypophysectomized animal was not due to the thyrotrophic hormone, as some had supposed, but to another specific substance which could be separated from the thyrotrophic hormone by virtue of its greater solubility in aqueous alcohol and the fact that it could be precipitated isoelectrically. Anselmino and others⁵⁹ and Friedgood⁶⁰ also showed that the corticotrophic is dis-

tinet from the thyrotrophic substance. The corticotrophic substance has no other known function than that of maintaining the cortex of the adrenal in a normal functioning condition.

Ketogenic Substance.—Since Burn and Ling⁶¹ first showed that a simple alkaline extract of anterior pituitary glands caused a greatly increased ketosis in rats on a butter diet, numerous investigations have been made on the subject. It has been my experience that almost any protein fraction obtained from anterior pituitary tissue may manifest ketogenic properties when administered to sensitive test objects such as the fasting rat or mouse. It has been found in growth extracts, in thyrotrophic extracts and in prolactin preparations. Very recently Neufeld and Collip⁶² have shown that the substance in pituitary extracts responsible for the ketogenic effect is thermostable over a certain pH range. It can be boiled, for example, in N/10 HCl without much loss in activity, and in this manner it can be differentiated from most other anterior lobe principles. All active ketogenic extracts cause an increase in the total lipid content of the liver.

Prolactin.—Prolactin appears to be purely a secretagogue to the fully developed mammary gland. Riddle and Bates⁶³ have shown that potent extracts containing this hormone can be prepared which are free of growth, thyrotrophic and gonadotrophic properties. White and others⁶⁴ have obtained a crystalline product which has only prolactin properties so far as they have been able to ascertain.

Diabetogenic Substance.—The property of anterior lobe extracts of inhibiting the hypoglycemic effect of insulin was first described by Houssay and Potlick⁶⁵ in hypophysectomized toads. A truly diabetogenic action of certain simple extracts of anterior lobe tissue was shown by Evans and others⁶⁶ in the dog. Shortly thereafter, Houssay and others⁶⁷ obtained similar results. More recently Young⁶⁸ has confirmed the diabetogenic action of freshly prepared crude extracts of fresh anterior lobe tissue. Young showed that the induced diabetic state persisted in some dogs after the cessation of injections. Campbell and Best⁶⁹ have been able to confirm Young's work. They also made the very important observation that the pancreas of a normal animal rendered diabetic by anterior pituitary extract treatment contained little or no insulin. Some points established by Young are worthy of special note: (1) Preparation and conservation of the extract at low temperature are essential. (2) Individuals of certain species (mouse, rat, and guinea pig) are almost completely insensitive to diabetogenic extracts effective in dogs. (3) The dog is the best animal in which to demonstrate the effect.

Young⁷⁰ has emphasized that the true diabetogenic activity of extracts should be clearly differentiated from simple hyperglycemic responses occurring within a few hours of the injection of the extract. The extracts which he has used successfully had little or no effect upon the blood sugar level within a few hours of injection.

The Glycotrophic Substance.—Certain anterior lobe extracts inhibit the hypoglycemic action of insulin and as a rule such extracts also cause an increase in muscle and liver glycogen. This latter action has been described as the glycotrophic effect by Young.⁷¹ In all probability this is the same as the so-called glycostatic effect of Russell and Bennett.⁷² These workers observed that the diminution in carbohydrate stores in hypophysectomized rats could be restored by appropriate treatment with anterior lobe extract.

The Specific Metabolic Principle.—Although this article deals specifically with anterior lobe principles, it would not be complete without reference to the substance present in all simple extracts of pituitary tissue, whole gland or dissected anterior and posterior lobes, which has the property of elevating the metabolic rate presumably by direct action in the periphery. So much attention has been paid by investigators in the field of pituitary physiology to the trophic principles that perhaps the importance of the pituitary as a source of active principles which are not trophic in function but which act directly upon certain phases of the metabolic processes has not been sufficiently stressed.

The early work of Houssay and Artundo⁷³ who found that in thyroidectomized dogs the metabolic effect of pituitary extracts, though reduced, was still present, of Gaebler^{51, 74} who demonstrated an increase in metabolism in thyroidectomized dogs treated with an anterior lobe extract, and of Riddle and associates⁵³ in which

an increased basal metabolic rate was obtained in thyroidectomized pigeons treated with a preparation of prolactin, showed that the metabolic rate could be elevated by anterior lobe extracts otherwise than by stimulation of the thyroid by the thyrotrophic substance. Extensive investigations have been made upon this metabolic stimulant within the past three years by my collaborators Drs. O'Donovan, Billingsley, Neufeld and Denstedt.^{52, 62, 75-92} The chief points of interest which have been established as a result of these investigations are: (1) The active principle is remarkably thermostable in aqueous solution. It has been boiled in 2 per cent NH_4OH for one hour with little loss in potency. It can be boiled in $\text{N}/10$ NaOH for a few minutes with comparative safety, but long heating in this alkaline medium has caused destruction of the active principle. Some activity has been observed by Dr. Denstedt in a preparation after boiling for ten hours in $\text{N}/4$ H_2SO_4 . The active principle has been successfully dialyzed and in electro dialysis experiments it has been found to migrate to the kathode cell. It is resistant to peptic digestion, but has been destroyed by prolonged treatment with trypsin.

(2) Injection of a potent preparation of this hormone into rabbits, guinea pigs, rats, or human subjects⁹³ has caused the metabolic rate to be sharply elevated for a period of a few hours following each injection. Our most extensive studies of this hormone have been made on normal, thyroidectomized and hypophysectomized rabbits. Associated with the increase in oxygen consumption in either fed or fasted animals, there is a depression in the respiratory quotient which is more marked in the former. This, together with other findings in connection with carbohydrate and nitrogen metabolism, suggests that the hormone specifically stimulates the metabolism of fat.

(3) Because of its close association with the melanophore-expending hormone of the pars intermedia, it is probably of pars intermedia origin. Recent work has shown that it is not identical with the melanophore hormone.^{90, 94} It has been differentiated from the ketogenic substance,^{62a} and also from the substance which antagonizes the hyperglycemic action of adrenalin.^{62b} This latter substance appears from our recent studies to be a posterior lobe principle separate and distinct from the well known oxytocin and vasopressin.

THE PREPARATION OF EXTRACTS

The alkaline extract of fresh anterior lobes first described by Evans,⁹⁵ and later modified slightly by others,⁹⁶ is an excellent starting point for the fractionation of the specific principles. Indeed, for much physiologic experimental work the simple alkaline extract, adjusted to a pH of about 7, at which point much protein material can be removed by centrifugation, is very satisfactory. Such an extract, though necessarily relatively dilute, contains some of practically all of the known active principles. All of these, so far as can be judged in the limited state of our knowledge at present, appear to be of protein nature or else so closely linked with protein as to be inseparable from protein substances. The preparation of physiologically pure or nearly physiologically pure hormone fractions has been accomplished by obtaining in various fractions, proteinlike material possessing slightly different physical properties. The methods by which anterior lobe material can be treated to prepare active extracts are innumerable. There are, however, a number of basic principles which should be adhered to in the preparation of any extract. These principles are:

1. The necessity of using fresh material. If this is not available, fresh glands that have been frozen and kept frozen until they are ready for use, or fresh glands that have been preserved in alcohol or acetone are moderately satisfactory. Dry powders prepared from defatted fresh glands, in vacuo and at low temperatures, are also quite good.
2. All of the known active principles are soluble in dilute aqueous alkali.
3. All of the active principles can be precipitated from aqueous solution on saturation with $(\text{NH}_4)_2(\text{SO}_4)$.
4. The growth principle, the gonadotrophic and thyrotrophic substances, are practically insoluble in high concentrations of neutral ethyl alcohol.
5. The corticotrophic principle, the thyrotrophic and gonadotrophic principles and prolactin are freely soluble in alkaline alcohol (70 per cent by volume).

6. All of the active principles which have been mentioned are insoluble in absolute alcohol.

7. The growth principle, one fraction of the thyrotrophic substance, prolactin and the corticotrophic hormones are all precipitable isoelectrically.

8. Gonadotrophic hormone cannot be precipitated isoelectrically. This is true also for one fraction of the thyrotrophic substance.

9. The growth principle can be adsorbed upon $\text{Ca}_3(\text{PO}_4)_2$ from neutral or slightly alkaline solutions and can be released by washing with ice-cold dilute aqueous alkali.

10. Practically all of the anterior lobe principles are more or less heat-stable over a definite pH range.

The methods of preparing and fractionating anterior lobe extracts are innumerable, and each worker in this field has his own preferences and dislikes in the matter of procedure. Often the same end result can be accomplished by entirely different methods of approach. Recently I have outlined the methods of extraction which I prefer to use in my own work.⁹⁷ I would make no claim, however, that these are better than those used successfully by others.

ANTIHORMONES

No discussion on anterior pituitary hormones would be complete without some reference to the subject of antihormones.

The fact has been known for many years that long-continued treatment of experimental animals with certain hormone preparations may lead to the development of a state of resistance to the physiologic effects of such extracts. This resistant state has been demonstrated, in the case of anterior lobe extracts, to the thyrotrophic,⁹⁸ the gonadotrophic,⁹⁹ the ketogenic,¹⁰⁰ and the growth effects^{9a} of certain extracts. Collip and Anderson¹⁰¹ showed that the blood serum of thyrotrophic hormone resistant animals contains a substance which is antagonistic to the thyrotrophic hormone and that previously untreated animals injected with blood serum containing this substance can be made resistant for a time to injections of extracts containing the thyrotrophic hormone. The existence of antigonadotrophic substances,^{99c, d, e, 102} an antiketogenic¹⁰³ and an antilactogenic¹⁰⁴ substance in the blood serum of animals chronically treated with appropriate extracts has been established.

As a possible explanation of such experimental results, Collip proposed the antihormone theory.^{9a, 105} This theory gives expression to the view that the antagonistic or inhibitory substance is a normal constituent of the blood and tissues; that there is a balance between a positively acting hormone substance and a hypothetical antagonist, the antihormone; and that it is only when this balance is greatly disturbed and the relative as well as absolute amount of antihormone is greatly increased that the latter can be detected. Many are of the opinion that all "antihormone" reactions are basically immunologic in type.^{106, 107} Undoubtedly, immunological reactions do play an important part in many of the antihormone reactions that have been described, since the extracts used contain protein which, even in the case of those made from the glands of the same species of animal as is used in testing,¹⁰⁸ may be considered as "foreign." Since antihormones have been shown to occur spontaneously in the blood serum of certain patients, and since there is evidence that the native secretion of the anterior lobe may be inhibited by the injection of antihormone serum,^{105b, 109} the exact significance of the antihormone reaction must remain to be disclosed by future work. The fact that pretreatment with certain hormones will cause the appearance in the blood of principles antagonistic to these hormones may be regarded as established beyond doubt.*

SUMMARY OF RECENT WORK

Before bringing this discussion to a close, I should like to report on the developments to date of work in my laboratory along somewhat new lines with certain pituitary extracts. It is impossible to state at this time the exact significance of certain observations which I shall describe.

1. Preliminary experiments to determine the effect of daily injections into chickens of a pituitary extract rich in the specific metabolic factor, carried out at Macdonald College with the cooperation of the Departments of Poultry and of Chemistry and under the supervision of Professors Maw and MacFarlane, have shown that such treatment may cause decolorization of the depot fat. This suggested that the metabolism of vitamin A might be influenced by the treatment. Already sufficient data have been obtained to show that significant changes in the vitamin A content of liver and blood may be produced by treatment of chickens in this manner. These results suggest that there may be a definite relationship between certain phases of pituitary activity and the metabolism of vitamin A.

2. A clinical trial of the same type of extract in a small group of obese women was undertaken by Dr. I. M. Rabinowitch. This was done since it had been shown that the specific metabolic hormone had similar effects on the metabolic rate and the respiratory quotient in man⁹³ as it had in rabbits.⁵² Some rather unexpected results were obtained. As a therapeutic aid to weight reduction in the cases studied no encouraging result was obtained. It so happened that most of the subjects treated had some degree of menstrual irregularity, and in four of eight cases treated the patients stated, without any leading question, that it was the first time in years that they had noted any regularity at all. Since the particular extract used had received heat treatment on a boiling water bath twice during its preparation at pH 5 and 10 and again during sterilization, there was little likelihood of any gonadotrophic or thyrotrophic principles surviving such treatment, and by actual test negative results have been obtained for these. The extract did contain a small amount of the substance which neutralizes the action of a standard gonadotrophic preparation when tested in the approved manner, namely by subcutaneous injection of the gonadotrophic substance and intraperitoneal injection of the antagonist. It has been proved also on test to have a high titre of corticotrophic substance. If it be assumed that the re-establishment of menstrual rhythm in the cases above mentioned was due to the treatment and that it was not fortuitous, the beneficial result might be attributed to a general improvement in metabolism due to the metabolic principle. It might equally well be attributed to the inactivated (by rat test) gonadotrophic substance in the extract or indeed to the antagonist. Since the latter is only active in the rat when administered intraperitoneally and since the patients were injected subcutaneously, it is difficult to understand how this might have been a factor.

I do not wish to appear to put undue emphasis on these observations, but in view of the fact that, on the whole, clinical experience with gonadotrophic preparations has been somewhat disappointing, it appears to me that many new avenues of treatment with new types of pituitary extracts should be explored. It is possible that the present method of standardizing gonadotrophic extracts in terms of rat units

*For an extensive review of the literature on this subject see Collip, Selye and Thomson, *Biological Reviews* (in press).

may be misleading and that clinical results may be obtained (as presumably they were in the cases mentioned) with specially prepared extracts which may be without visible effect on the ovaries of the normal rat. A clinical trial of standardized extracts of corticotrophic and specific metabolic principles is now being undertaken and the results of these experiments may throw some further light on the etiology of certain types of menstrual disorders.

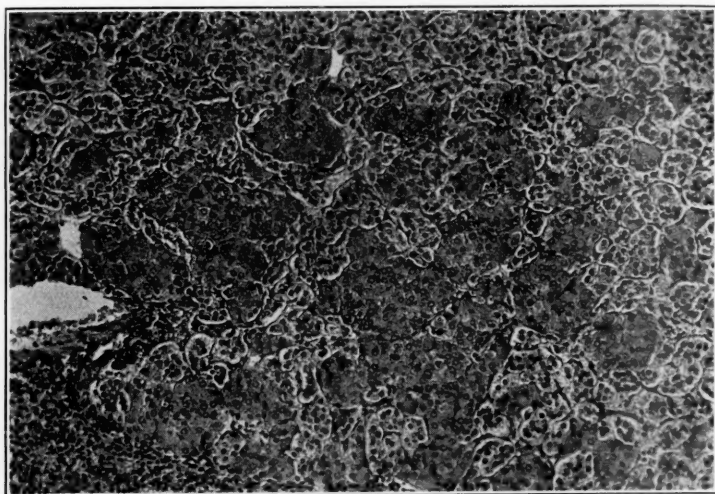


Fig. 1.—High power of adrenal medulla of an hypophysectomized rat treated for sixteen days with the medullotrophic extract by feeding. Note the hypertrophy of the "dark cells".

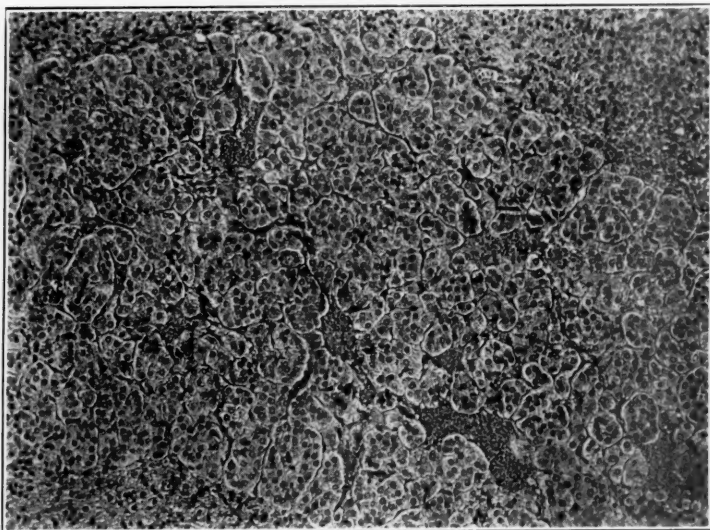


Fig. 2.—High power of adrenal medulla of an hypophysectomized rat treated for nine days with a corticotrophic preparation by subcutaneous injection. Both cortex and medulla are comparable to similar tissues in normal animals.

3. Probably the most important of the investigations relating to the physiology of the pituitary in which I have been interested has been my recent finding of a medullotrophic principle in primary alcoholic extracts of prime gland tissue.¹¹⁰ This principle has also the remarkable quality of being orally active. It would appear from the investigations which I have so far been able to make with it, to be trophic to the so-called "dark cells" of the adrenal medulla. The diagnostic test for the active substance consists in the production of hypertrophy

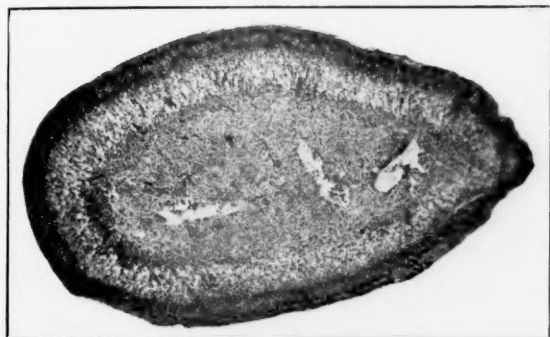


Fig. 3.—Cross section of adrenal of hypophysectomized rat showing atrophy of cortex and hypertrophy of dark cells of medulla. This is a low power photomicrograph of same section as shown in high power in Fig. 1.



Fig. 4.—Cross section of adrenal gland of hypophysectomized rat treated with corticotrophic hormone. This is same section as shown in high power in Fig. 2.

of these special cells in the medulla of hypophysectomized rats. This test can also be used to assay the potency of different preparations. It is in many respects similar to the test used in this laboratory for corticotrophic hormone. In this latter test the restoration of the atrophic cortex of the hypophysectomized rat toward or to normal forms the basis for assay of corticotrophic extracts. In my earliest experiments on the differentiation of the corticotrophic from the medullotrophic hormone I was able to demonstrate in hypophysectomized

rats treated with a corticotrophic preparation by injection, complete restoration of the cortex with no visible change in the medulla and in other hypophysectomized animals treated with the medullotrophic preparation by mouth no appreciable change in the atrophic cortex but a strong positive reaction in the nature of hypertrophy of the



Fig. 5.—Atrophic thyroid of hypophysectomized rat treated with medullotrophic hormone; from same animal as shown in Fig. 1.

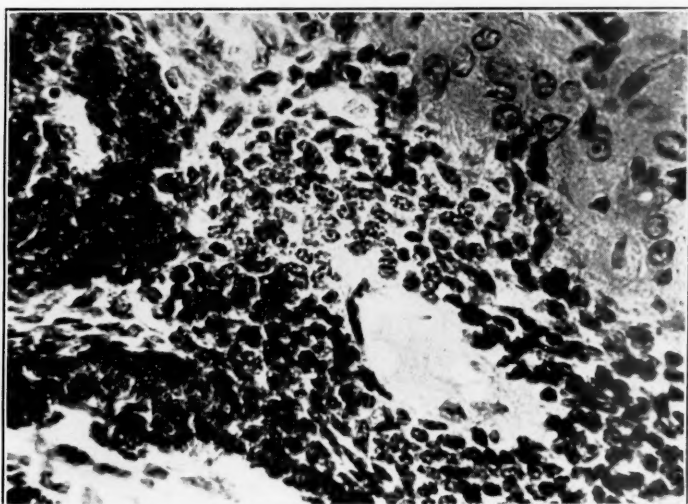


Fig. 6.—Atrophic ovary with wheel cells of hypophysectomized rat treated with medullotrophic hormone; from same animal as Fig. 1.

dark cells of the medulla (see Figs. 1 to 6). Clinicians, I am sure, will be interested to know that it was upon clinical evidence obtained following the oral administration of a certain extract that I was testing that I became convinced that an active principle was concerned. Sub-

stantiation of this conviction was realized when the medullotrophic action of the extract was established in hypophysectomized rats treated by the oral route. All of the evidence so far available would seem to show that this orally active pituitary principle does not act upon the chromaffin system. The intensive and fruitful work which has been going on for some years now in many laboratories upon problems of adrenal physiology and chemistry serves to show how very complex are the functions of the adrenal gland. The close association between the adrenal cortex and the gonads has long been recognized, as has also the relationship of the medulla to the sympathetic nervous system. It would appear from the experimental studies described in brief above that the medulla may have still another function subserved through its so-called dark cells. Since potent preparations of the corticotrophic hormone satisfactory for administration by injection to the human subject can now be made, and since the medullotrophic substance can be administered safely by the oral route, the clinician will have two agents, each of which can be biologically standardized, with which to influence at least two functions of the adrenal glands.

REFERENCES

- (1) *Van Dyke, H. B.*: The Physiology and Pharmacology of the Pituitary Body, Vol. I, 1936, Univ. of Chicago Press. (2) *Idem*: The Physiology and Pharmacology of the Pituitary Body, Vol. II, 1939, Univ. of Chicago Press. (3) Sex and Internal Secretion, edited by E. Allen, 1939, Williams and Wilkins, Vol. II. (4) *Carlson, A. J.*: See *Van Dyke, H. B.* The Physiology and Pharmacology of the Pituitary Body, Vol. I Foreword, 1936, Univ. of Chicago Press. (5) *Collip, J. B., Selye, H., and Thomson, D. L.*: Virchows Arch. f. path. Anat. **290**: 23, 1933. (6) *Selye, H., Mortimer, H., Thomson, D. L., and Collip, J. B.*: Arch. Pathol. **18**: 878, 1934. (7) *Jeffers, K. R.*: Am. J. Anat. **56**: 257, 1935. (8) (a) *McEuen, C. S., and Thomson, D. L.*: Brit. J. Exper. Path. **14**: 384, 1933. (b) *Ball, H. A., and Samuels, L. T.*: Am. J. Cancer **16**: 351, 1932. (c) *Idem*: Ibid. **18**: 380 (June) 1933. (9) (a) *Collip, J. B.*: J. Mt. Sinai Hosp. **1**: 28, 1934. (b) *Evans, H. M.*: Proc. Assoc. Research Nerv. & Ment. Dis., December, 1936. (c) *Lyons, W. E.*: Proc. Soc. Exper. Biol. & Med. **35**: 645, 1937. (d) *Moon, H. D.*: Ibid. **35**: 649, 1937. (10) *Mortimer, H.*: Radiol. **28**: 5, 1937. (11) *Collip, J. B., Selye, H., and Thomson, D. L.*: Proc. Soc. Exper. Biol. & Med. **30**: 544, 1933. (12) *Lee, M. O., and Schaffer, N. K.*: J. Nutrition **7**: 337, 1934. (13) (a) *Geesink, A., and Koster, S.*: Nederl. tijdschr. v. geneesk. **2**: 6155, 1928. (b) *Hogben, L., Charles, E., and Slome, D.*: J. Exper. Biol. **8**: 345, 1931. (c) *Pugsley, L. I., and Anderson, E. M.*: Am. J. Physiol. **109**: 85, 1934. (14) (a) *Silberberg, M.*: Proc. Soc. Exper. Biol. & Med. **32**: 1423, 1935. (b) *Silberberg, M., and Silberberg, R.*: Am. J. Path. **15**: 55, 1939. (15) *Freud, J., Levie, L. H., and Kroon, D. B.*: J. Endocrinol. **1**: 56, 1939. (16) *Rogowitsch, N.*: Beitr. f. path. Anat. u. z. allg. Path. **4**: 453, 1888-89. (17) *Adler, L.*: Arch. f. Entwcklungsmechn. d. Organ. (Roux's) **39**: 21, 1914. (18) *Gudernatsch, J. F.*: Ibid. **35**: 457, 1913; Am. J. Anat. **15**: 431, 1914. (19) *Allen, B. M.*: Biol. Bull., Woods Hole **36**: 405, 1919. (20) *Smith, P. E., and Smith, I. P.*: J. M. Research **43**: 267, 1922. (21) *Spaul, E. A.*: Brit. M. J. **2**: 1 and 48, 1927. (22) *Uhlenhuth, E., and Schwartzbach, S.*: Anat. Rec. **34**: 119, 1926. (23) *Smith, P. E.*: J. A. M. A. **88**: 158, 1927. (24) *Foster, G. L., and Smith, P. E.*: Ibid. **87**: 2151, 1926. (25) *Cushing, H.*: Brit. M. J. **2**: 1 and 48, 1927. (26) *Loeb, L., and Bassett, R. B.*: Proc. Soc. Exper. Biol. & Med. **26**: 860, 1929. (27) *Aron, M.*: Compt. rend. Soc. de biol. **102**: 682, 1929. (28) *Janssen, S., and Loeser, A.*: Arch. f. exper. Path. u. Pharmacol. **163**: 517, 1931. (29) *Watrin, J., and Florentin, P.*: Compt. rend. Soc. de biol. **110**: 1161, 1932. (30) *Grab, W.*: Arch. f. exper. Path. u. Pharmacol. **167**: 313, 1932. (31) *Junkmann, K., and Schoeller, W.*: Klin. Wehnschr. **11**: 1176, 1932. (32) *Benedict, E. B., Putnam, T. J., and Teel, H. M.*: Am. J. M. Sc. **179**: 489, 1930. (33) *Houssay, B. A., Biasotti, A., and Magdalena, A.*: Rev. Soc. Argent. de biol. **8**: 130, 1932. (34) *Schittenhelm, A., and Eisler, B.*: Klin. Wehnschr. **11**: 6, 1932. (35) *Baumann, E. J., and Marine, D.*: Proc. Soc. Exper. Biol. & Med. **29**: 1220, 1932. (36)

- Riddle, O., and Polhemus, I.: *Am. J. Physiol.* **98**: 121, 1931. (37) Noether, P.: *Klin. Wehnschr.* **11**: 1072, 1932. (38) Schockaert, J. A.: *Am. J. Anat.* **49**: 379, 1932. (39) Anderson, E. M., and Collip, J. B.: *Proc. Soc. Exper. Biol. & Med.* **30**: 680, 1933. (40) Eitel, H., Krebs, H. A., and Loeser, A.: *Klin. Wehnschr.* **12**: 615, 1933. (41) Marine, D., and Rosen, S. H.: *Am. J. Physiol.* **107**: 677, 1934. (42) Siebert, W. J., and Smith, R. S.: *Ibid.* **95**: 396, 1930. *Proc. Soc. Exper. Biol. & Med.* **27**: 622, 1930. (43) Verzar, F., and Wahl, V.: *Biochem. Ztschr.* **240**: 37, 1931. (44) Schittenhelm, A., and Eisler, B.: *Klin. Wehnschr.* **11**: 1092, 1932. (45) Loeb, L., and Friedman, H.: *Proc. Soc. Exper. Biol. & Med.* **29**: 648, 1932. (46) Loeser, A.: *Arch. f. exper. Path. u. Pharmacol.* **163**: 530, 1931. (47) Schockaert, J. A., and Foster, G. L.: *J. Biol. Chem.* **95**: 89, 1932. (48) Closs, K., Loeb, L., and MacKay, E. M.: *Ibid.* **96**: 585, 1932. (49) Grab, W.: *Arch. f. exper. Path. u. Pharmacol.* **167**: 413, 1932. (50) Anderson, E. M., and Collip, J. B.: *J. Physiol.* **82**: 11, 1934. (51) Gaebler, O. H.: *Am. J. Physiol.* **110**: 584, 1935. (52) O'Donovan, D. K., and Collip, J. B.: *Endocrinology* **23**: 718, 1938. (53) Riddle, O., Smith, G. C., Bates, R. W., Moran, C. S., and Lahr, E. L.: *Ibid.* **20**: 1, 1936. (54) Smith, P. E., and Engle, E. T.: *Am. J. Anat.* **40**: 159, 1927. (55) Zondek, B., and Aschheim, S.: *Arch. f. Gynäk.* **130**: 1, 1927. (56) Fenning, E. M., Henry, J. S., and Browne, J. S. L.: *Canad. M. A. J.* **36**: 83, 1937. (57) Smith, P. E.: *Am. J. Anat.* **45**: 205, 1930. (58) Collip, J. B., Anderson, E. M., and Thomson, D. L.: *Lancet* **2**: 347, 1933. (59) Anselmino, K. J., Hoffmann, F., and Herold, L.: *Klin. Wehnschr.* **12**: 1944, 1933. (60) Friedgood, H. B.: *Endocrinology* **20**: 159, 1936. (61) Burn, J. H., and Ling, H. W.: *Quart. J. Pharm. & Pharmacol.* **6**: 31, 1933. (62) a. Neufeld, A. H., and Collip, J. B.: *Canad. M. A. J.* **40**: 535, 1939. b. *Ibid.* **40**: 537, 1939. (63) Riddle, O., and Bates, R. W.: *Endocrinology* **17**: 689, 1933. (64) (a) White, A., Catchpole, H., and Long, C. N. H.: *Science* **86**: 82, 1937. (b) Shipley, R. A., Stern, K. G., and White, A.: *J. Exper. Med.* **69**: 785, 1939. (65) Houssay, B. A., and Potlick, D.: *Compt. rend. Soc. de biol.* **101**: 940, 1929. (66) Evans, H. M., Meyer, K., Simpson, M. E., and Reichert, F. L.: *Proc. Soc. Exper. Biol. & Med.* **29**: 857, 1932. (67) Houssay, B. A., Biasotti, A., di Benedetto, E., and Rietti, C. T.: *Compt. rend. Soc. de biol.* **112**: 497, 1933. (68) (a) Young, F. G.: *Lancet* **2**: 372, 1937. (b) Richardson, K. C., and Young, F. G.: *Lancet* **1**: 1098, 1938. (69) Campbell, Jas., and Best, C. H.: *Am. J. Physiol.* **123**: 30, 1938. (70) Young, F. G.: *J. Physiol.* **87**: 13, 1936. (71) *Idem*: *Ibid.* **90**: 20, 1937. (72) Russell, J. A., and Bennett, L. L.: *Proc. Soc. Exper. Biol. & Med.* **34**: 406, 1936. (73) Houssay, B. A., and Artundo, A.: *Compt. rend. Soc. de biol.* **114**: 391, 1933. (74) Gaebler, O. H.: *J. Exper. Med.* **57**: 349, 1933. (75) O'Donovan, D. K., and Collip, J. B.: *West. J. Surg.* **45**: 564, 1937. (76) O'Donovan, D. K., and Collip, J. B.: *Canad. M. A. J.* **39**: 83, 1938. (77) Neufeld, A. H., and Collip, J. B.: *Ibid.* **39**: 83, 1938. (78) Denstedt, O. F., and Collip, J. B.: *Ibid.* **39**: 84, 1938. (79) O'Donovan, D. K., Neufeld, A. H., Denstedt, O. F., and Collip, J. B.: *Canad. Physiol. Soc. Meeting*, May 23, 1938. (80) Denstedt, O. F., O'Donovan, D. K., and Neufeld, A. H.: *Am. J. Physiol.* **123**: 52, 1938. (81) Neufeld, A. H., and Collip, J. B.: *Ibid.* **123**: 155, 1938. (82) O'Donovan, D. K., and Collip, J. B.: *Ibid.* **123**: 157, 1938. (83) Neufeld, A. H., and Collip, J. B.: *Endocrinology* **23**: 735, 1938. (84) Billingsley, L. W., O'Donovan, D. K., and Collip, J. B.: *Ibid.* **24**: 63, 1939. (85) Collip, J. B.: *Proc. North Side Br. Chicago Med. Soc.*, Apr. 6, 1939. (86) Collip, J. B.: *Proc. Assn. Am. Physic.*, Atlantic City Meeting, May 2, 1939. (87) Collip, J. B., Neufeld, A. H., and Denstedt, O. F.: *Proc. Soc. Study of Internal Secretions*, St. Louis Meeting, May 12, 1939. (88) Collip, J. B., Neufeld, A. H., and Denstedt, O. F.: *Proc. Am. Assn. for Study of Goiter*, Cincinnati Meeting, May 22, 1939. (89) Collip, J. B., Neufeld, A. H., and Denstedt, O. F.: *Proc. Am. Med. Assn.*, St. Louis Meeting, May 18, 1939. (90) Denstedt, O. F., and Collip, J. B.: *Am. J. Physiol.* **126**: 476, 1939. (91) Neufeld, A. H., and Collip, J. B.: *Ibid.* **126**: 592, 1939. (92) Collip, J. B.: *West. J. Surg.* **47**: 1, 1939. (93) Rabinowitch, I. M., Mountford, M., O'Donovan, D. K., and Collip, J. B.: *Canad. M. A. J.* **40**: 105, 1939. (94) Teague, R. S.: *Proc. Soc. Exper. Biol. & Med.* **40**: 516, 1939. (95) Evans, H. M.: *Harvey Lectures*, Philadelphia, 1925, J. B. Lippincott Co. **19**: p. 212. (96) Burn, J. H., and Ling, H. W.: *J. Physiol.* **64**: 22, 1927. (97) Collip, J. B.: *Cyclopedia of Medicine* **11**: 637, 1939. (98) Loeb, L., and Friedman, H.: *Proc. Soc. Exper. Biol. & Med.* **29**: 172, 1931. (99) (a) Zondek, B.: *Die Hormone des Ovariums und des Hypophysenvorderlappens*, Berlin, 1931, J. Springer. (b) McPhail, M. K.: Quoted by Collip, J. B.: *Internat. Clin.* **4**: 51, 1932. (c) Selye, H., Collip, J. B., and Thomson, D. L.: *Proc. Soc. Exper. Biol. & Med.* **31**: 487, 1934. (d) Selye, H., Collip, J. B., and Thomson, D. L.: *Ibid.* **31**: 566, 1934. (e) Selye, H., Bachman, C.,

Thomson, D. L., and Collip, J. B.: *Ibid.* 31: 1113, 1934. (100) Black, P. T., Collip, J. B., and Thomson, D. L.: *J. Physiol.* 82: 385, 1934. (101) Collip, J. B., and Anderson, E. M.: *Lancet* 1: 76, 1934. (102) Bachman, C., Collip, J. B., and Selye, H.: *Proc. Soc. Exper. Biol. & Med.* 32: 544, 1934. (103) Black, P. T.: *J. Physiol.* 84: 15, 1935. (104) Young, F. G.: *Biochem. J.* 32: 656, 1938. (105) (a) Collip, J. B.: *Ann. Int. Med.* 8: 10, 1934. (b) Collip, J. B.: *Ibid.* 9: 150, 1935. (106) (a) Max, P., Schmeckebier, M. M., and Loeb, L.: *Endocrinology* 19: 329, 1935. (b) DuShane, G. P., Levine, W. T., Pfeiffer, C. A., and Witschi, E.: *Proc. Soc. Exper. Biol. & Med.* 33: 339, 1935. (c) Twombly, G. H.: *Endocrinology* 20: 311, 1936. (d) Werner, S. C.: *Proc. Soc. Exper. Biol. & Med.* 34: 392, 1936. (107) Collip, J. B., Selye, H., and Thomson, D. L.: *Biological Reviews*. In press. (108) Collip, J. B.: *Canad. M. A. J.* 36: 199, 1937. (109) Parkes, A. S., and Rowlands, I. W.: *J. Physiol.* 88: 305, 1936. (110) Collip, J. B.: *Canad. M. A. J.* 42: 2, 1940.

BLOOD LIPIDS IN PREGNANCY*

OTTO H. SCHWARZ, M.D., S. D. SOULE, M.D., AND BERNICE DUNIE, A.B.,
ST. LOUIS, MO.

(From the Washington University School of Medicine, Department of Obstetrics and Gynecology, the St. Louis Maternity Hospital and Barnes Hospital)

FAT metabolism in the adult, male or female, has presented some interesting problems. Leathes and Raper¹ in their monograph, "The Fats," discuss the synthesis of fat in animals. It is very difficult to demonstrate the formation of fat from protein. Direct evidence of a transformation of carbohydrate into fat has not been obtained in any organ. Also, the carbohydrates differ so greatly from the fats in chemical characteristics and composition that it is unlikely that the processes of transformation of carbohydrate into fat would be demonstrated easily experimentally. Furthermore, with the understanding of the processes of digestion, absorption, and intermediate metabolism, the problems of lipid synthesis from protein and carbohydrate lose much of their practical interest.

The developing product of conception presents a distinct lipid problem. The growing fetus has a definite lipid requirement for essential cell growth. This question of fat synthesis in the fetus or fat transportation across the placental barrier is a problem of magnitude comparable to that which confronted observers who solved the problems involved in fat metabolism in the adult.

It is interesting to review the facts that the fetus begins to store fat at about the same stage of gestation that the Langhans layer of cells begins to disappear from the placenta, and at about the same time that the blood lipids are beginning to show a general increase in concentration in the maternal circulation.

With the advent of a microtechnique² for determination of blood lipids, a steadily increasing literature has developed.

Until recently the studies in this phase of biologic chemistry which have been concerned with pregnancy have not been sustained. No

*Presented at the Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 7 to 9, 1939.

effort has been made on the part of one observer to carry the problem through in the same patient from onset of pregnancy, through labor and the puerperium. Truly, excellent observations have been made for individual members of the group of lipids through pregnancy. Detailed studies are available for individual patients at term, in labor, and during the puerperium. Boyd³ presents a most complete picture of the lipemia of pregnancy at term. We have not found published any complete lipid studies on the same individual from the early weeks of pregnancy through gestation.

Numerous observers have demonstrated the so-called lipemia of pregnancy and Bloor and later Boyd have discussed the similarity of this lipemia to changes in blood lipids associated with various constitutional disease conditions. It is not within the province of this present discussion to go into the origin of the lipemia of pregnancy. Rather, we should like to present our findings as a preliminary study of blood lipids during normal pregnancy. From various clues we have obtained in this study we expect to carry this work further, possibly adding something to the question of how the fetus gets its lipids.

Most of the literature concerning lipids in pregnancy has to do with cholesterol studies. Hermann and Neumann⁴ reported an increase of blood cholesterol esters during pregnancy. Slemons and Curtis⁵ reported an absence of cholesterol esters in fetal blood when no anesthesia was employed and concluded that the placenta was impermeable to this fraction of blood lipid. Slemons and Stander⁶ showed that the large quantity of fat in maternal blood was not associated with a corresponding change in the circulation of the fetus and further concluded that the placenta was impermeable to fat and lipid. Gardner and Gainsborough⁷ reported that free cholesterol increases during pregnancy to the thirtieth week with a decrease in ester cholesterol to about the same time. In their series, there occurs then, a reversal of curve so that at parturition approximately a normal relationship exists again. Kaufmann and Mühlboeck⁸ do not note this fluctuation but report little variation from the second month of gestation to term. Plass and Tompkins⁹ reported total and lipid phosphorus much higher in maternal than fetal blood serum; they also note that sex and birthweight have no influence on blood phosphorus. These observers feel that fats and lipids are probably synthesized in the fetal organism. Mühlboeck¹⁰ concludes that from the fourth month to term there is a progressive increase in iodine-combining power which is similar to the hyperlipemia of pregnancy, indicating an increase in unsaturation of the fatty acids during pregnancy.

Boyd³ has shown that the red blood cells show no marked variation in lipid composition during pregnancy. The significant changes in lipid concentrations of the blood are noted in the blood plasma or serum. Boyd demonstrated that the total lipids of blood plasma during pregnancy are increased on the average to one-half as high again as in the nonpregnant. All of the component lipids are increased, the greatest increase being in neutral fat. Phospholipid, free and ester cholesterol are each higher than their pregestational value. The normal ratios between phospholipid, ester and free cholesterol are but slightly altered. Phospholipid and free cholesterol are each increased about 25 per cent; ester cholesterol only about 9 per cent higher. The iodine numbers of total and phospholipid fatty acids are similar in pregnancy to those of the nongravid female.

Comparisons of mean values may or may not warrant valid deductions. With the use of standard deviation formulas, sound conclusions may be drawn. Our information is presented in two forms. The graphs demonstrate the trend of concentration of the various lipid constituents through gestation and in the puerperium. It will be noted that

the normal variations in concentration of lipids are great. With such a range of normal, the curve of progressive change throughout a whole pregnancy is of more importance than relationship of the patient's particular findings to an average.

The group of tables presents the detailed findings of each patient throughout her particular pregnancy. Significant points of history are added. It is from these tables that subsequent items of importance may be found.

The human subject is selected for this study because of the variable response of experimental animals, and the constant doubt as to the

TABLE I. BLOOD SERUM LIPIDS IN PREGNANCY

NUMBER 35617	DURATION OF PREGNANCY					DE-LIVERY	POST PARTUM	PER-CENTAGE INCREASE
	12 WK.	18 WK.	24 WK.	29 WK.	35 WK.			
Total lipid	481	639	765	780	851	779	639	77
Neutral fat	123	210	226	170	252	176	142	105
Total fatty acid	290	385	453	447	525	462	367	81
Total cholesterol	127	194	239	238	222	210	193	88
Ester cholesterol	93	135	171	173	154	147	135	86
Free cholesterol	34	60	68	65	68	63	58	100
Phospholipid	169	145	186	256	275	296	215	75
Pl. F. A. I ₂ No.	102		117	108	110	113		
T. F. A I ₂ No.	103	112	105	99	101	107		
Total fatty acid to Phospholipid	1.71	2.65	2.43	1.35	1.90	1.56	1.71	
Phospholipid to Total cholesterol	1.33	0.74	0.77	1.08	1.23	1.40	1.11	
Ester cholesterol to Total cholesterol	0.73	0.69	0.71	0.72	0.69	0.70	0.70	

Negro, 19 yr., gravida i, estimated date of confinement Aug. 17, 1939, delivered Aug. 3, 1939, weight gain 27 pounds from eleventh week. R.B.C. 3,370,000, Hb. 75 per cent. Urine negative. Labor 11 $\frac{1}{4}$ hours. Seminarcosis: Dilaudid-Hyoscine. Baby: 2,480 gm., breast fed. Anesthesia: 15 c.c. of CHCl₃, 50 c.c. of ether.

TABLE II. BLOOD SERUM LIPIDS IN PREGNANCY

NUMBER 21747	DURATION OF PREGNANCY			DELIVERY	POST PARTUM	PER-CENTAGE INCREASE
	20 WK.	33 WK.	40 WK.			
Total lipid	672		1006	911	791	50
Neutral fat	155		309	249	210	100
Total fatty acids	390	577	623	551	472	60
Total cholesterol	200	210	268	247	224	35
Ester cholesterol	140	142	197	172	156	40
Free cholesterol	60	68	71	75	68	25
Phospholipid	224	189	297	300	253	34
Pl. F. A. I ₂ No.		96	99	100		
T. F. A. I ₂ No.	107	90	93	101		
Total fatty acid to Phospholipid	1.74	3.00	2.09	1.83	1.87	
Phospholipid to Total cholesterol	1.12	0.90	1.10	1.21	1.13	
Ester cholesterol to Total cholesterol	0.70	0.67	0.73	0.69	0.69	

Patient, white, 27 years, gravida ii, estimated date of confinement June 5, 1939, delivered June 10, 1939, weight gain 22 pounds from twentieth week. R.B.C. 4,370,000, Hb. 80 per cent. Urine negative. Labor 5 $\frac{1}{2}$ hours. Seminarcosis: Seconal-Hyoscine. Baby: 3,720 gm., breast fed. Anesthesia: 4 c.c. of CHCl₃ for delivery.

ability to assign comparable results in the human being. The principle followed in this work was to do a complete lipid chemistry at monthly intervals on a series of eight pregnant women. These studies in most instances were carried out as planned; in two or three cases fewer observations are available than anticipated.

This study is as yet incomplete. All but one patient has delivered but post-partum examinations are as yet not available on all subjects.

TABLE III. BLOOD SERUM LIPIDS IN PREGNANCY

NUMBER 22373	DURATION OF PREGNANCY					DELIVERY	POST PARTUM	PER-CENTAGE INCREASE
	14 WK.	19 WK.	23 WK.	30 WK.	35 WK.			
Total lipid	766	810	844	878	992	1051		37
Neutral fat	152	267	220	218	317	368		142
Total fatty acids	436	488	503	523	622	679		53
Total cholesterol	234	252	240	245	252	248		8
Ester cholesterol	173	180	169	177	180	176		4
Free cholesterol	61	72	70	68	73	72		20
Phospholipid	264		272	297	302	318		20
Phospholipid fatty Acid I ₂ No.	104		121	80	92	121		
Total fatty acid I ₂ No.	117	100	107	102	99	92		
Total fatty acid } Phospholipid }	1.65		1.85	1.76	2.08	2.13		
Phospholipid } Total cholesterol }	1.12		1.13	1.21	1.19	1.28		
Ester cholesterol } Total cholesterol }	0.74	0.71	0.70	0.72	0.71	0.71		

Negro, 18 years, gravida i, estimated date of confinement Aug. 22, 1939, delivered Aug. 16, 1939, weight gain 18 pounds from fourteenth week. R.B.C. 3,600,000, Hb. 60 per cent. Urine negative. Labor 22¾ hours. Seminarcoisis: Seconal—Hyoscine. Baby: 3,890 gm., breast fed. Anesthesia: 15 c.c. of CHCl₃, 88 c.c. of ether.

TABLE IV. BLOOD SERUM LIPIDS IN PREGNANCY

NUMBER 35368	DURATION OF PREGNANCY					PRE-MATURE DELIVERY	POST PARTUM	PER-CENTAGE INCREASE
	12 WK.	18 WK.	21 WK.	26 WK.	30 WK.			
Total lipid	540	659	761	788	873	1103	666	104
Neutral fat	122	205	245	219	233	335	121	174
Total fatty acids	316	385	459	476	525	687	371	117
Total cholesterol	154	220	230	216	245	282	211	83
Ester cholesterol	106	156	159	147	182	201	151	90
Free cholesterol	48	64	71	70	63	81	60	70
Phospholipid	194		180	255	275	353	234	81
Pl. F. A. I ₂ No.	79		66	62	114	94		
T. F. A. I ₂ No.	105	106	100	104	109	95		
Total fatty acid } Phospholipid }	1.62		2.55	1.86	1.90	1.94	1.58	
Phospholipid } Total cholesterol }	1.26		0.78	1.18	1.12	1.25	1.10	
Ester cholesterol } Total cholesterol }	0.68	0.70	0.69	0.68	0.74	0.71	0.71	

Patient, white, 22 years, gravida i, estimated date of confinement Aug. 21, 1939, delivered July 10, 1939. Premature twins. Labor 10 hours and 55 minutes. Weight gain 20 pounds from twelfth week. Urine negative. R.B.C. 3,780,000, Hb. 80 per cent. Seminarcoisis: Seconal, Morphia, Hyoscine. Babies: 1,650 gm., 1,820 gm., no breast. Anesthesia: 6 c.c. of CHCl₃, 80 c.c. of ether.

The women in this series were selected without special regard for age, color, parity, or habitus. They were all patients in the out-patient department. Their habitual diet was not supervised beyond the usual dietary instructions given all prenatal cases. Blood was drawn between 2:00 and 3:00 P.M., during usual clinic hours. The patients were not requested to refrain from food. Man and Gildea¹¹ have not found any relation between variations in serum lipids and changes in body weight, food intake, hemoconcentration, the menstrual period or season of the year. Boyd¹² notes that in normal man a consistent and significant

TABLE V. BLOOD SERUM LIPIDS IN PREGNANCY

NUMBER 31075	DURATION OF PREGNANCY					DELIVERY	POST PARTUM	PER-CENTAGE INCREASE
	18 WK.	23 WK.	28 WK.	38 WK.	42 WK.			
Total lipid	860	904	1123	1170	1222	1305	1148	52
Neutral fat	190	265	259	298	451	384	329	137
Total fatty acids	510	543	654	692	793	805	702	58
Total cholesterol	233	270	332	342	291	342	311	42
Ester cholesterol	172	202	240	253	206	243	226	47
Free cholesterol	61	68	92	89	85	99	85	62
Phospholipid	322		372	361	343	417	357	30
Pl. F. A. I ₂ No.			111	107		100		
T. F. A. I ₂ No.		110	107	99		88		
Total fatty acid	1.58		1.75	1.91			1.97	
Phospholipid								
Phospholipid	1.38		1.12	1.05			1.15	
Total cholesterol								
Ester cholesterol	0.72		0.72	0.74			0.73	
Total cholesterol		0.74						

Patient, white, 20 years, gravida ii, estimated date of confinement July 17, 1939, delivered Aug. 9, 1939, weight gain 26 pounds from eighteenth week. R.B.C. 4,520,000, Hb. 80 per cent. Urine negative. Labor 4 hours and 35 minutes. Seminarsis: Seconal—Hyoscine. No anesthesia. Baby: 3,540 gm., breast fed.

TABLE VI. BLOOD SERUM LIPIDS IN PREGNANCY

NUMBER 25943	DURATION OF PREGNANCY						DE-LIVERY	POST PARTUM	IN-CREASE, %
	18 WK.	23 WK.	27 WK.	31 WK.	34 WK.	38 WK.			
Total lipid	699	821	894	940	920	940	908	513	34
Neutral fat	206	262	297	241	222	246	272	84	44
Total fatty acid	435	513	565	561	540	567	566	281	30
Total cholesterol	177	276	225	266	270	260	229	168	56
Ester cholesterol	126	161	156	194	198	197	166	124	57
Free cholesterol	51	55	69	72	72	63	63	45	41
Phospholipid	232	235	267	303	296	302	296	180	31
Pl. F. A. I ₂ No.	89	84	90	93	96	96	107		
T. F. A. I ₂ No.	106	98	99	102	99	97	95		
Total fatty acid	1.87	2.18	2.11	1.85	1.82	1.87	1.91		
Phospholipid									
Phospholipid	1.31	1.09	1.18	1.14	1.49	1.16	1.29		
Total cholesterol									
Ester cholesterol	0.71	0.74	0.69	0.72	0.73	0.75	0.72		
Total cholesterol									

Patient, white, 24 years, gravida ii, estimated date of confinement June 17, 1939, delivered June 17, 1939, weight gain 24 pounds from eighteenth week. Urine negative. Labor 5¼ hours. Seminarsis: None. Baby: 4,080 gm., breast fed. Anesthesia: 7 c.c. of CHCl₃ for delivery.

TABLE VII. BLOOD SERUM LIPIDS IN PREGNANCY

NUMBER 35633	DURATION OF PREGNANCY								DELIVERY	POST PARTUM	PERCENTAGE INCREASE
	11 WK.	15 WK.	19 WK.	23 WK.	27 WK.	32 WK.	37 WK.	40 WK.			
Total lipid	554	638	879	875	1049	1038	1221	1205	1167	943	122
Neutral fat	169	170	187		219	270	267	297	246	246	76
Total fatty acid	337	380	501		601	602	710	709	662	554	108
Total cholesterol	156	185	275	293	314	332	363	355	368	286	136
Ester cholesterol	110	136	204	210	222	242	274	264	268	209	150
Free cholesterol	46	49	71	83	92	90	88	91	100	77	113
Phospholipid	158	192	280	367	368		408	377	374	272	160
Pl. F. A. I ₂ No.	61	63	91		94		92		101		
T. F. A. I ₂ No.	98	102	93	121	107	99	101		104		
Total fatty acid	} 2.13	1.98	2.14		1.63		1.74	1.88	1.77	2.04	
Phospholipid											
Phospholipid											
Total cholesterol	} 1.01	1.03	1.01	1.25	1.14		1.12	1.06	1.01	0.95	
Ester cholesterol											
Total cholesterol	} 0.70	0.73	0.74	0.71	0.70	0.72	0.75	0.74	0.73	0.73	

Patient, white, 18 years, gravida ii, estimated date of confinement Aug. 1, 1939, delivered Aug. 5, 1939, weight gain 29 pounds from eleventh week. R.B.C. 4,750,000, Hb. 85 per cent. Urine: Trace of sugar last month. Seminarcosis: Seconal—Morphia—Hyoscine. Baby: 3,170 gm., breast fed. Labor 13½ hours. Anesthesia: CHCl₃ 6 c.c., ether 45 c.c.

post-prandial lipemia is not produced until the amount of ingested fat reaches 200 gm.

The method used in these analyses is that described by Boyd¹³ with several minor changes of our own. This technique is the most recently published modification of Bloor's^{2, 14} micromethod of lipid determinations. Iodine numbers were calculated as suggested by Yasuda¹⁵ and complemented by Boyd.¹⁶

RESULTS

Graphs 1 to 4, inclusive, demonstrate the variations of the individual members of the blood serum lipids throughout pregnancy from the first sample through the puerperium. On these graphs are charted the findings of each patient for each constituent lipid.

All serum lipids show a steady increase in value from the first observation to term. The increment of all these serum lipids is essentially a gradual one. Even with neutral fat, which is stored late in gestation, there is no abrupt rise in the latter months of pregnancy.

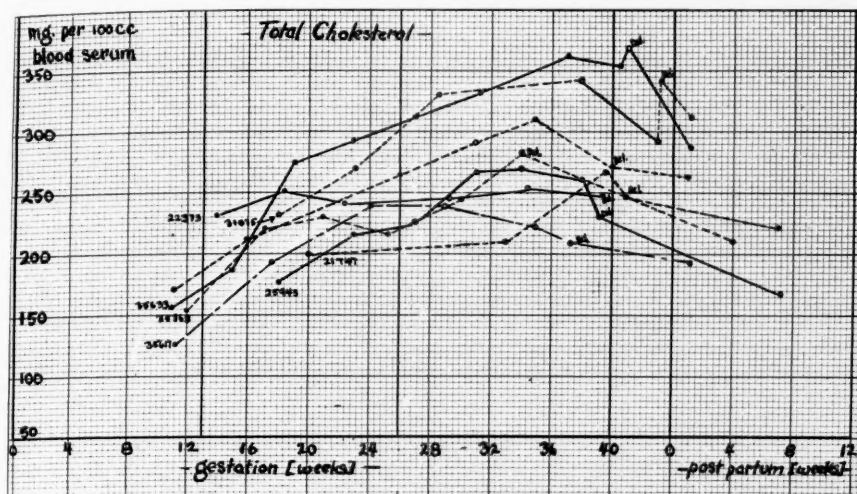
Tables I to VII, inclusive, give a composite picture for each patient. Here again we note a great variation in values for the same serum lipid among the various subjects.

The percentage increase for total lipids varied from 34 to 122 per cent; of neutral fat, from 44 to 172 per cent; of total fatty acids, from 30 to 117 per cent; of total cholesterol, from 8 to 136 per cent; of ester cholesterol, from 4 to 150 per cent; of free cholesterol, from 20 to 113 per cent; of phospholipid, from 20 to 160 per cent.

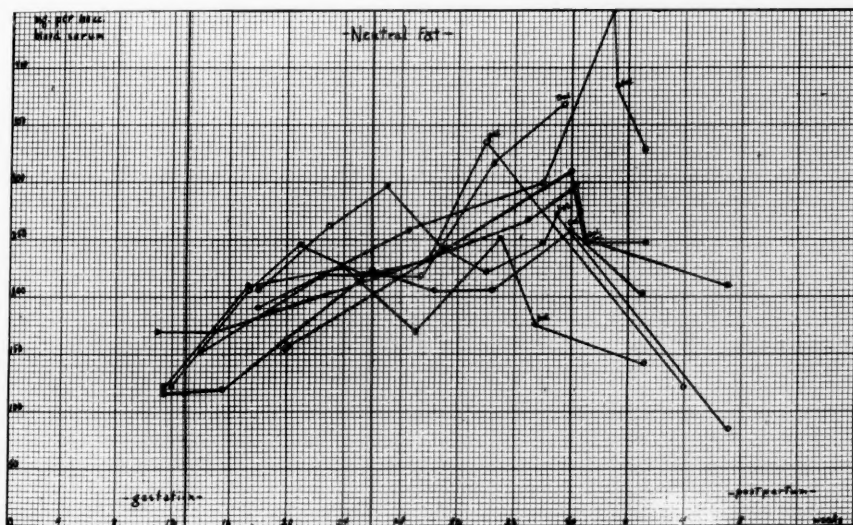
Neutral fat values showed the greatest percentage increase at term, compared to the first calculations in early pregnancy in six of seven sets of calculations.

These findings are essentially in accord with variations in the various lipid values in normal, nonpregnant individuals.

Boyd¹⁷ records normal plasma neutral fat values of from none to 773 mg. per cent; phospholipid of 21 to 510 mg. per cent; free cholesterol of 5 to 136 mg. per cent. Thus the important information is the curve of value of the various lipids for each subject rather than the individual value of a lipid fraction.



Graph 1.



Graph 2.

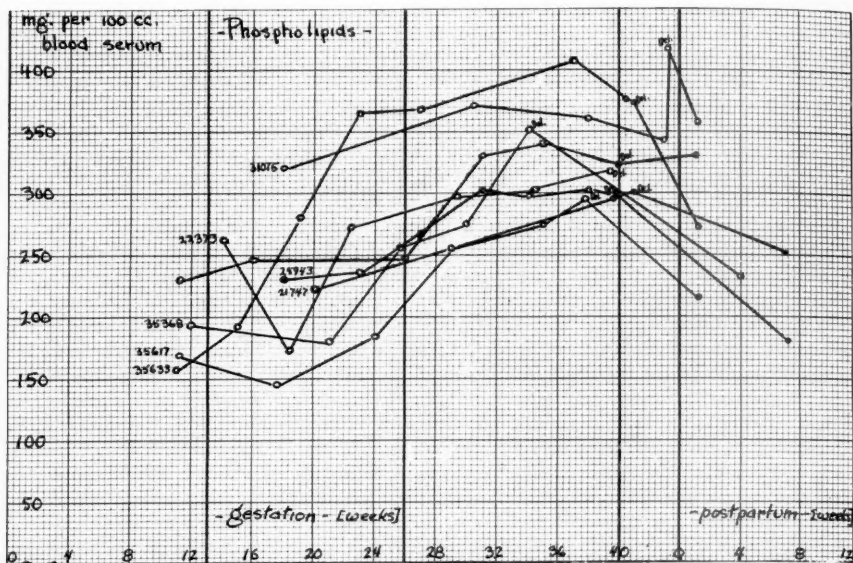
In some instances the delivery specimen demonstrated a decreased value over the last previous calculation.

No apparent relation can be attributed to gain in weight, hemoglobin concentration, duration of labor, seminarcosis, or anesthesia.

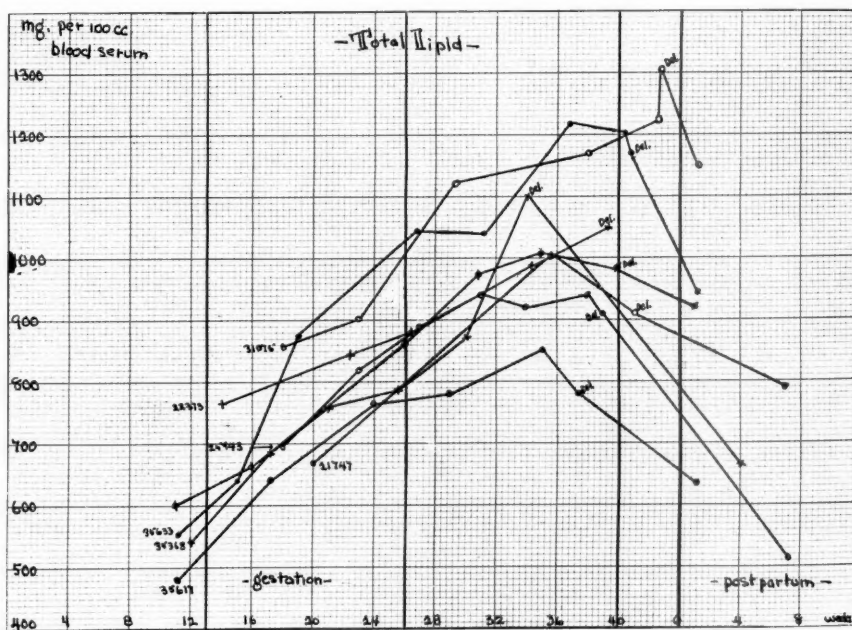
Neutral fat in 6 of 7 sets of determinations showed the greatest percentage increase in value.

Free and ester cholesterol are noted to be increased in value in the blood serum during pregnancy. In 5 of 7 patients the ester cholesterol was uniformly higher in percentage increase throughout gestation; in two cases the free cholesterol was higher.

The ratio of ester cholesterol : total cholesterol remained remarkably constant throughout pregnancy in all patients.



Graph 3.



Graph 4.

There is a rise in phospholipid similar in percentage to that of cholesterol.

The phospholipid : total cholesterol ratio is of special interest because of the antagonistic behavior of these two elements as observed in several biologic processes. No consistent change in this ratio is noted with the progress of pregnancy.

Phospholipid fatty acid iodine numbers and total fatty acid iodine numbers, indices to the degree of unsaturation of these respective factors, show some variations. These changes are not within any range as to warrant a conclusion as to any degree of change in saturation of the fatty acids. The ratio of total fatty acids: phospholipid has been considered to be of general importance in lipid metabolism because of the relation between these two factors during fat absorption.

DISCUSSION

The results discussed at this time are in the nature of a preliminary report. The changes in blood serum lipid concentration from early pregnancy to term are reported. Findings in fetal cord blood serum and in the puerperium will be recorded at a subsequent time.

The close organic relationship of certain members of the lipid group to substances which are of great significance in obstetrics and gynecology is recognized. The organic structure of cholesterol is closely related to that of the estrogens, progesterone, and ergosterol. Phospholipid and cholesterol balance is one to warrant close consideration. The antagonism of these two lipids is extremely interesting and may play an important role in obstetrics. The hydrophilic and hydrophobic properties of these two substances have not been considered extensively by the clinician¹⁸.

Boyd¹⁷ notes that human plasma contains about the same amount of fatty substances as it does of inorganic salts and much more lipid than of water-soluble organic compounds such as the nitrogenous derivatives and glucose. The lipids of plasma are exceeded only by the albumins and globulins in amount present and are about equal in concentration to that of fibrinogen.

The relation of this relatively large concentration of lipids to colloidal osmotic pressure of plasma and to the genesis of edema warrants further study.

CONCLUSIONS

Blood serum lipids were studied at frequent intervals in a series of normal women from early pregnancy through parturition and in the puerperium.

A lipemia is noted in pregnancy. It is characterized by a most marked increase in neutral fat and a lesser increment in cholesterol fractions and phospholipid.

The rise in lipid content is gradual through gestation.

No significant changes in unsaturation of the phospholipid fatty acids or total fatty acids were noted.

The ester cholesterol: total cholesterol ratio remains remarkably constant throughout pregnancy.

The phospholipid: total cholesterol ratio exhibited was quite variable but no constant change was noted.

No apparent relation of weight gain, weight of the baby, hemoconcentration, seminarcosis, or anesthesia was noted.

A decrease in all lipid elements was noted frequently, but not constantly, at delivery.

A subsequent report will discuss fetal cord blood serum lipids and blood serum lipids in the puerperium.

REFERENCES

- (1) *Leathes, J. B., and Raper, H. S.*: Monographs in Biochemistry: The Fats, New York, 1925, Longmans, Green & Co. (2) *Bloor, W. R.*: J. Biol. Chem. **77**: 531, 1928. (3) *Boyd, E. M.*: J. Clin. Investigation **13**: 347, 1934. (4) *Hermann, E., and Neumann, J.*: Biol. Ztschr. **43**: 47, 1912. (5) *Slemons, J. M., and Curtis, C. S.*: AM. J. OBST. & GYNEC. **75**: 569, 1917. (6) *Slemons, J. M., and Stander, H. J.*: Johns Hopkins Hosp. Bull. **34**: 7, 1923. (7) *Gardner, J. A., and Gainsborough, H.*: Lancet **1**: 603, 1929. (8) *Kaufmann, C., and Mühlbock, O.*: Ztschr. f. d. ges. exper. Med. **89**: 200, 1933. (9) *Plass, E. D., and Tompkins, H.*: J. Biol. Chem. **56**: 309, 1923. (10) *Mühlbock, O.*: Monatschr. f. Geburtsh. u. Gynäk. **105**: 53, 1937. (11) *Man, E. B., and Gildea, E. F.*: J. Biol. Chem. **119**: 769, 1937. (12) *Boyd, E. M.*: Ibid. **110**: 61, 1935. (13) *Idem*: Am. J. Clin. Path. **8**: 77, 1938. (14) *Bloor, W. R.*: J. Biol. Chem. **82**: 273, 1929. (15) *Yasuda, M.*: Ibid. **94**: 401, 1931. (16) *Boyd, E. M.*: Ibid. **101**: 323, 1933. (17) *Idem*: Canad. J. Research **15**: 1, 1937. (18) *Sinclair, R. G.*: Physiol. Rev. **14**: 351, 1934.

DISCUSSION

DR. E. D. PLASS, IOWA CITY, IOWA.—At our last meeting one of the blood lipids, cholesterol, was introduced by Drs. Colvin and Bartholomew into their discussion of the etiology of the toxemias of pregnancy. Their findings indicated that the whole blood of toxemic patients had a higher concentration of total cholesterol than that of normal women at corresponding periods of gestation. They then postulated a cholesterol vascular change as predisposing to the placental infarction, which they believe to be of etiologic significance.

On the other hand, the paper which we have just heard deals only with the changes in the various determinable fat fractions of the blood serum during the course of normal pregnancy. Each of the women studied showed gradual increases in the several lipid constituents up to the time of delivery, even though there was no consistent and significant alteration in the degree of unsaturation of either the phospholipid fatty acids or the total fatty acids. The significance of this lipemia is not clear, but it must be viewed as part of the normal metabolic response to pregnancy.

The liver plays a dominant role in fat metabolism, and the question naturally arises as to whether the detected alterations in the serum lipids during normal pregnancy are consistent with hepatic malfunction, which has long been postulated but never clearly proved. Data concerning the variations in human liver disease unassociated with jaundice are conflicting, but a recent and still unpublished study by Levine indicates that there is a decrease in the unsaturation of the various fatty acids and in both the total and the esterified cholesterol. On the basis of these findings it seems reasonable to conclude that the fat metabolizing ability of the liver is not diminished by pregnancy. Such negative evidence serves to strengthen the belief that deficient hepatic function is not a conspicuous part of the metabolic changes incident to gestation, and that the importance attached to this organ as a possible cause of certain of the complications of pregnancy was unjustified.

DR. JAMES R. BLOSS, HUNTINGTON, W. VA.—I wish to report two additional patients who have shown positive Wassermanns and were also positively hypoeudocrine. These two, together with three previously reported, became negative immediately upon the change of the lochia. All five of the babies of these patients were negative, both from the cord and from blood taken from their heels. I cannot explain this phenomenon other than by some change in the blood cholesterol of these hypoeudocrine patients.

DR. JAMES E. DAVIS, ANN ARBOR, MICH.—May I ask Dr. Soule if any check has been made upon the lipid level and the gonadotropic levels in the patients he has studied? In pregnancy there is normally an increase of anabolic activity, and there is a very great difference in the constitutional reaction of different individuals to pregnancy. The lipoids and the cholesterol are increased, and generally the gonadotropic level is also increased. In thyroid hypofunction and pituitary hyperfunction, the blood lipoids are changed.

DR. SOULE (closing).—Basal metabolisms were run on two of these eight patients and were normal.

There is a great possibility that there is some such relationship between the gonadotropic hormones and lipids. There is also a close relationship of certain members of the lipid group organically. Cholesterol and progesterone, estrin and ergosterol, are all closely related structurally.

Phospholipids and cholesterol balances also require close observation. The hydrophilic and hydrophobic properties of these substances have not been studied enough by the clinician. The relation of this relatively large concentration of lipids to colloidal osmotic pressure of plasma and to the tendency to edema is another problem which warrants further study.

VULVOVAGINAL MYCOSES IN PREGNANCY*

WITH THE RELATION OF SYMPTOMS TO GENERA AND SPECIES OF FUNGI

BAYARD CARTER, M.D., CLAUDIUS P. JONES, R. A. ROSS, M.D., AND
WALTER L. THOMAS, M.D., DURHAM, N. C.

(From the Department of Obstetrics and Gynecology, Duke University School of Medicine and Duke Hospital)

PREGNANCY as a predisposing factor in the occurrence of yeastlike fungi in the vagina and on the vulva is becoming generally well recognized. Carter and Jones¹³ in 1937 studied the vaginal flora of 114 apparently normal pregnant patients and of 100 apparently normal gynecologic patients. Yeastlike fungi were isolated from 32 per cent of the 114 pregnant patients and from 14 per cent of the 100 gynecologic patients.

Much of the confusion regarding mycotic vulvovaginitis is due to the inability to identify the genera and species of yeastlike fungi isolated from the vagina and vulva. Lack of systematic methods of study and classification and the fact that yeastlike fungi are frequently isolated from apparently normal vulvas and vaginas have added to the existing confusion. Jones and Martin¹⁶ and Martin, Jones, Yao, and Lee¹⁴ published a method of classifying yeastlike fungi isolated from the vagina. This method of classification was based upon the study of 68 freshly isolated vaginal strains. All of the strains were classified as belonging to the genus *Cryptococcus* or to 1 of 5 species of *Monilia*,† including a new and previously undescribed species, *Monilia stellatoidea*.

*Presented at the Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 7 to 9, 1939.

Aided by grants from the John and Mary R. Markle Foundation and the Research Council, Duke University.

†The generic name *Monilia* is not the correct name for the mycelial forming, non-ascosporogenous yeastlike fungi. It has been used in this paper in preference to any of the several generic names that have been applied to this group. Recent papers by Langeron and Guerra, Didders and Lodder, and Ciferri and Redaelli show a tendency to adopt a single generic name for these fungi and it is hoped that some agreement may be reached and terms universally adopted.

At the present time there have been classified by the method described 294 vaginal and vulval strains; 68 as previously reported,¹⁶ 75 isolated from patients with symptoms of mycotic vulvovaginitis (unpublished), and 151 strains which form the material for this report.

In previous studies,^{13, 16} no effort was made to correlate the patient's history and the clinical findings with the occurrence of yeastlike fungi in the vagina. The present study was undertaken to determine in a series of 200 pregnant patients, (1) the incidence of yeastlike fungi on the vulva as compared to the incidence in the vagina; (2) the relation of the patient's symptoms and the findings on vulval and vaginal examination to the species of yeastlike fungi isolated from the vulva and vagina; (3) the possibility of any degree of correlation existing between the presence of agglutinins in the patient's serum, skin sensitivity, and positive cultures; (4) the incidence of trichomonads in patients with yeastlike fungi; and (5) the relation of the vaginal smear types to the presence of yeastlike fungi or trichomonads.

HISTORICAL

According to Castellani,¹ Wilkinson in 1840 (Lancet 1: 1840) was the first to report yeastlike organisms in the vaginal discharge. Few attempts were made, however, to study any number of vaginal strains until 1924 when Castellani and Taylor³ described vaginal *Monilia* and vaginal moniliases. Plass, Hesseltine, and Borts⁵ in 1931 found *Monilia* in 12 of 18 pregnant patients who had vaginal irritation, a percentage of 66.7. In a control group of 46 pregnant women without symptoms, *Monilia* were demonstrated in 15 patients, 32.6 per cent. These authors also found that monilia vaginitis in pregnancy was a definite source of infection with oral thrush of the newborn. Bland and others,¹⁵ 1937, found pregnancy to be a predisposing factor in the production of mycotic vulvovaginitis. By vaginal inoculations with strains of *Monilia* from patients with varying degrees of symptoms, they were able to infect pregnant women in a higher percentage of instances than they were able to infect the nonpregnant women. These investigators also noted that experimental inoculation was least successful in patients with profuse discharge. This observation is interesting to us, because in our own series many of the patients from whom both *Monilia* and trichomonads were recovered were diagnosed clinically trichomoniasis prior to the establishment of the diagnosis by the routine outlined in this study.

Studies of the vaginal monilias have also been made by Popoff, Ford and Cadmus,⁴ 1929, by Hesseltine,⁷ 1933, by Hopkins and Hesseltine,^{11, 12} 1936, and by Weinstein and Wickerham,¹⁹ 1938.

MATERIAL

The race, marital status, parity, and the duration of pregnancy of the patients studied are shown in Table I. The 54 white patients were unmarried and confined to a maternity home. The 146 colored patients were regularly attending the outpatient prenatal clinic. Most of the patients were of a low economic status. The only criterion used in the selection of the patients for study was no past history or complaint of pruritus, discharge, or irritation prior to pregnancy. The patients with these complaints were excluded from the series.

METHOD OF STUDY

History.—A special mimeographed history sheet was used throughout the study. The same questions were asked each patient. No leading questions were asked. No effort was made in taking the patient's history to differentiate degrees of pruritus, discharge, or irritation. The patient was simply asked if itching had been experienced or discharge had increased with pregnancy, or if irritation was or had been present. Whereas the inadequacy of this method is realized, only in this manner did we feel that we could get comparable results.

TABLE I

RACE	WHITE	NUMBER
	COLORED	54
Age	10-19	146
	20-29	93
	30-39	82
	40-49	23
		2
Marital	Married	112
	Single	88
Approximate month of pregnancy	2-3	2
	3-4	11
	4-5	10
	5-6	34
	6-7	59
	7-8	84
Parity	Primiparas	83
	Multiparas	117

Vaginal Examination.—The impression from the character of the discharge, vaginal mucosa, cervix, etc., was recorded without knowledge of the cultural or hanging drop findings. The impression from the vaginal examination was limited to one or more of four things: mycotic vulvovaginitis, trichomoniasis, cervicitis, or negative findings. A diagnosis of mycotic vulvovaginitis from the vaginal examination meant, white, flaky or cheesy discharge, thrushlike patches, etc.; of trichomoniasis, frothy, bubbly or purulent discharge, or the presence of punctate red spots on the cervix or vaginal mucosa, said to be characteristic of the condition. Doubtful patients were classed as negative. Patients thought to be within normal limits were classed as negative.

Vaginal Cultures.—Cultures from the vagina were taken at the time of the vaginal examination. After the insertion of a sterile unlubricated speculum, a swab was used to collect any suspicious material from the vaginal walls, posterior fornix or cervix. Immediately after collection, the collected material from the swab was planted on a Sabouraud's agar slant and was grown at room temperature.

Labial Cultures.—All of the labial cultures were collected on swabs moistened with Sabouraud's broth. At the time of collection the swabs were removed from the broth, and cultures were taken from between the labial folds and around the vulva. The swabs were then reinserted into the broth and the culture grown for twenty-four hours at room temperature before plating on Sabouraud's agar plates.

Fresh Preparation for Trichomonads and Yeasts.—Two vaginal swabs were placed in 1 c.c. of normal saline and fresh preparations were examined immediately for the presence of yeastlike organisms or trichomonads. The time consumed in the examination of the fresh preparation was not prolonged and represented on the average four or five minutes.

Smears.—Smears were made of the vaginal discharge of each patient and stained with Gram's stain. Each smear was classified into 1 of 3 types as previously described by Carter and Jones,¹³ 1937, a slight modification of the method first described by Schroder,² 1921.

Type 1. Vaginal bacilli alone or vaginal bacilli with yeasts.

Type 2. Vaginal bacilli with other organisms.

Type 3. No vaginal bacilli.

Whereas it is realized that certain objections to this method are valid, we do feel that with some experience one may predict from the study of vaginal smears the predominant types of organisms which might be encountered if complete cultures were done.

Agglutinations.—From one-half of the 200 patients in the series, blood was drawn from the median basilic vein, allowed to clot, the serum removed, and used for agglutinations. Antigen was prepared from stock strains of the 5 species of *Monilia* isolated previously from the vagina by one of us (C. P. J.). The antigen was prepared by washing off into saline the twenty-four-hour growth of the fungus on Sabouraud's agar. The saline suspensions of the fungus were precipitated by centrifugation in Hopkin's vaccine tubes. Dilution of the antigen was 1:1000 by volume of packed cells. The method of agglutinations consisted in shaking for thirty minutes in a mechanical shaking machine, placing in the refrigerator over night, and reshaking for thirty minutes before reading.

Intradermal Tests.—One hundred of the 200 patients in the series were tested for skin sensitivity to antigens prepared from stock strains of the 5 species of vaginal *Monilia*. Antigen for intradermal testing was prepared in the same manner as antigen used for agglutinations, with the exception that the fungi were heat killed, and 0.35 per cent tricesol was added as a preservative. For testing, 0.1 c.c. of each of the 5 antigens was injected intradermally in the forearm. Readings of the intradermal tests were made in twenty-four to forty-eight hours.

Classification of the Fungi.—Detailed methods of classification of the yeastlike fungi have been described previously by Jones and Martin,¹⁶ 1938, and Martin, Jones, Yao and Lee,¹⁴ 1937.

After growth on Sabouraud's agar, yeastlike colonies were picked and inoculated into Sabouraud's broth. After forty-eight hours the broth was shaken and streaked on beef extract blood agar plates. From the blood agar plates only the smooth typical colonies were selected for study. Rough or variant colonies were considered the result either of contamination by bacteria, or of complete or partial dissociation and not within the scope of this report. The method as previously described consisted of observation of the growth in Sabouraud's broth at forty-eight hours, study of colony characteristics on beef extract blood agar, carbohydrate fermentations, observations of morphology on corn meal agar, the production of ascospores on carrot plugs and rabbit pathogenicity tests.

RESULTS

Incidence.—Yeastlike fungi belonging to either the genus *Monilia*, *Saccharomyces* or *Cryptococcus* were isolated from 86, or 43 per cent, of the 200 patients studied. Eleven, or 20.4 per cent, of the 54 white patients and 75, or 51.4 per cent, of the 146 colored patients showed positive cultures from either the vagina or labia, or both. If positive labial cultures are disregarded, 66, or 33 per cent, of the patients had positive vaginal cultures.

Vaginal and labial cultures showed the same fungus in 62 patients. Four patients had positive vaginal cultures with negative labial cultures. Cultures of the external genitalia were positive in 21 patients in whom no fungi were recovered from the vagina. In 2 patients 2 distinct species of yeastlike fungi were cultured from the labial folds.

Our inability to recover several species of yeastlike fungi from a larger number of patients was probably due to the similarity of the colonies of the different species on Sabouraud's agar.

Classification.—The carbohydrate fermentations of the 124 strains classed as of the genus *Monilia* are shown in Table II. In Table III the carbohydrate fermentations of the strains classed as *Cryptococci* and *Saccharomyces* are shown.

As in a previous report, Jones and Martin,¹⁶ the majority of the strains belonged to the species *Monilia stellatoidea*. The second largest group was *Monilia albicans*. Twenty-seven of the strains isolated belonged to the genera *Saccharomyces* and *Cryptococcus*.

Rabbit Pathogenicity Tests.—Each strain identified as *M. albicans* was tested for pathogenicity when inoculated intravenously into rabbits. The method described by Benham⁶ and Stovall and Pessin⁸ was used. For intravenous injection 1 c.c. of a 1 per cent saline suspension of the organisms was used. In each rabbit, death occurred in from one to five days. In the rabbits which survived for as long as two or three days, macroscopic lesions were demonstrable in the kidneys and in

TABLE II. *MONILIA* FERMENTATIONS

	NUMBER OF STRAINS	DEX- TROSE	SAC- CHAROSE	LACTOSE	MALTOSE	RABBIT PATHOGE- NICITY
<i>Stellatoidea</i> vagina	35	AG*	-	-	AG	-
<i>Stellatoidea</i> labia	35	AG	-	-	AG	-
<i>Albicans</i> vagina	17	AG	A	-	AG	+
<i>Albicans</i> labia	20	AG	A	-	AG	+
<i>Candida</i> vagina	2	AG	AG	-	AG	Not done
<i>Candida</i> labia	1	AG	AG	-	AG	Not done
<i>Krusei</i> vagina	2	AG	-	-	-	Not done
<i>Krusei</i> labia	4	AG	-	-	-	Not done
<i>Parasilosis</i> vagina	1	AG	-	-	-	Not done
<i>Parasilosis</i> labia	7	AG	-	-	-	Not done
Totals	124					

*AG, Acid and gas. A, Acid. -, Negative.

TABLE III. GENUS *SACCHAROMYCES* AND *CRYPTOCOCCUS*

	NUMBER OF STRAINS	DEXTROSE	SAC- CHAROSE	LACTOSE	MALTOSE
<i>Saccharomyces</i> vagina	1	AG*	AG	-	-
<i>Saccharomyces</i> labia	1	AG	AG	-	-
<i>Saccharomyces</i> vagina	1	AG	AG	-	AG
<i>Saccharomyces</i> labia	1	AG	AG	-	AG
<i>Cryptococcus</i> vagina	3	AG	-	-	-
<i>Cryptococcus</i> labia	3	AG	-	-	-
<i>Cryptococcus</i> vagina	2	A	-	-	-
<i>Cryptococcus</i> labia	5	-	-	-	-
<i>Cryptococcus</i> vagina	2	AG	AG	-	AG
<i>Cryptococcus</i> labia	4	AG	AG	-	AG
<i>Cryptococcus</i> vagina	1	AG	AG	AG	-
<i>Cryptococcus</i> labia	1	AG	AG	AG	-
<i>Cryptococcus</i> vagina	1	AG	AG	-	-
<i>Cryptococcus</i> labia	1	AG	AG	-	-
Total	27				

*AG, Acid and gas. A, Acid. -, Negative.

many rabbits in other organs. On injection of the more highly pathogenic strains, many rabbits failed to survive this length of time and in these animals the fungi could be cultured from the kidneys.

Each strain identified as *M. stellatoidea* was tested by the intravenous injection in rabbits of 2 c.c. of a 1 per cent suspension (this dose was twice the lethal dose used for *M. albicans*). In no rabbits did death occur.

RELATION OF SYMPTOMS AND VAGINAL FINDINGS TO THE GENERA AND SPECIES OF FUNGI

The incidence of the various genera and species of yeastlike fungi, the findings in the fresh preparations in that group of patients, the patients' histories regarding itching, discharge and irritation, and the impression from the vaginal examinations are shown in Tables IV, V, and VI. The findings in each group will be discussed separately. In our experience the predominant symptom of mycotic vulvovaginitis is pruritus. Patients with uncomplicated mycotic vulvovaginal infections rarely complain of excessive discharge. However, multiple infections are common and this is especially true in the colored pregnant females.

Any evaluation of pruritus, discharge, or irritation, must of necessity include consideration of trichomonads and of bacterial infections. Although patients in this series complained of both pruritus and discharge when neither fungi nor trichomonads could be recovered from the vagina, only yeastlike fungi and the protozoa will be considered etiologic agents in this report. Many patients were diagnosed from the character of the discharge as having trichomoniasis when trichomonads were not found in the hanging drop. This finding lends some support to the idea that certain bacteria may produce a vaginitis which cannot be differentiated clinically from that caused by trichomonads. A more complete report on trichomoniasis of pregnancy is to be published later.

Monilia albicans.—Ten (50 per cent) of the 20 patients with positive vaginal or labial cultures for *M. albicans* complained of pruritus. Seven of the 10 showed both trichomonads and *Monilia*. A diagnosis of mycotic vulvovaginitis from the vaginal examination was recorded in only 4 of the 20 patients with positive cultures; 3 of the 4 complained of pruritus.

TABLE IV

		MONILIA	
		ALBICANS	STELLATOIDEA
		NUMBER	
Incidence	Patients with positive cultures	20	38
	Positive vaginal cultures	17	35
	Positive labial cultures	20	35
	Positive labia and vagina	17	32
Fresh preparation	Trichomonads	10	24
	Yeast	8	16
History	Itching	10	15
	Discharge	13	17
	Irritation	2	0
Impression from the vaginal examination	Trichomoniasis	8	14
	Mycotic	4	11
	Cervicitis	7	8
	Negative	5	14

Monilia stellatoidea.—The number of patients with pruritus in the 38 from whom *Monilia stellatoidea* was cultured was 15, or 39.4 per cent. Twelve of the 15 patients with pruritus showed trichomonads in addition to the fungus. That is, a multiple infection occurred in all but 3 of the patients complaining of pruritus. Seventeen of the 38 patients complained of increased discharge; 10 of the 17 were in the group complaining also of pruritus. A diagnosis of mycotic infection from the vaginal examination was made in 3 patients, of moniliasis plus trichomoniasis in 4 patients. Three patients who complained of neither pruritus nor discharge were diagnosed from the vaginal examination as mycotic infections.

M. (parasitosis) parakrusei,* *M. (candida) tropicalis** and *M. Krusei*.—*M. (parasitosis) parakrusei*: Of 7 patients with positive cultures, in only 1 was the fungus recovered from the vagina. In this patient there was no complaint of pruritus or discharge. Two of the 7 patients were diagnosed as trichomoniasis and the diagnosis was confirmed by hanging drop. In no patient was a diagnosis of mycotic infection justified from the patient's history or the vaginal findings.

*Since the work of Martin, Jones, Yao and Lee in which 6 species of *Monilia* were described, Langeron and Guerra have shown that the species *candida* and *tropicalis* are identical and have adopted *tropicalis* as the species name. Likewise *parasitosis* and *parakrusei* were found to be identical and the species name *parakrusei* is to be preferred. Therefore *Monilia candida* should become *Monilia tropicalis* and *Monilia parasitosis* should become *Monilia parakrusei*.

TABLE V

		MONILIA		
		PARA-SILOSI	CANDIDA	KRUSEI
		NUMBER		
Incidence	Patients with positive cultures	7	2	4
	Positive vaginal cultures	1	2	2
	Positive labial cultures	7	1	4
	Positive labia and vagina	1	1	2
Fresh preparation	Trichomonads	2	1	1
	Yeast	0	2	1
History	Itching	0	1	0
	Discharge	4	0	2
	Irritation	0	0	0
Impression from the vaginal examination	Trichomoniasis	2	0	0
	Mycotic	0	1	0
	Cervicitis	2	0	0
	Negative	3	1	0

M. (candida) tropicalis: Of the 2 patients with positive cultures for *M. (candida) tropicalis*, 1 complained of pruritus and the impression from the vaginal examination was mycotic vulvovaginitis. The second patient had no complaint and the impression was negative. *M. Krusei*: Of the 4 patients positive for *M. Krusei*, 2 were positive from the labia only and 2 from the labia and vagina. None of the 4 patients complained of pruritus, and all were diagnosed from the vaginal examination as negative.

GENUS CRYPTOCOCCUS

Of 14 patients with positive cultures for the simple yeastlike organisms belonging to the genus *Cryptococcus*, only 7 were positive in both the vaginal and labial cultures and 7 from the labia only. Of the 14 patients 2 complained of pruritus vulvae. In 1 patient with pruritus, *M. albicans* and trichomonads were both present in addition to the *Cryptococcus*. The second patient with pruritus also had trichomonads. In none of the 14 patients did the vaginal examination show evidence of a mycotic infection. In only 1 patient were the fungi demonstrable without culture.

The outstanding clinical finding in these patients was some degree of cervicitis in 8 of the 14. That the fungi were related in any way to the cervicitis is doubtful. Benham⁹ and others have shown that *Cryptococci* occur frequently on the normal skin, around the nails, etc.

TABLE VI

		GENUS	
		SACCHA-ROMYCES	CRYPTOCOC-CUS
		NUMBER	
Incidence	Patients with positive cultures	2	14
	Positive vaginal cultures	2	7
	Positive labial cultures	2	7
	Positive labia and vagina	2	7
Fresh preparation	Trichomonads	0	4
	Yeast	0	1
History	Itching	0	2
	Discharge	0	6
	Irritation	0	0
Impression from the vaginal examination	Trichomoniasis	0	3
	Mycotic	0	0
	Cervicitis	1	8
	Negative	1	5

Further work must be done to determine, if any, the role played by *Cryptococci* in the production of vaginal pathologic change.

GENUS SACCHAROMYCES

True ascosporeogenous yeastlike fungi from the standpoint of vaginal pathology are relatively unimportant. Though the patients reported here are insufficient for drawing conclusions, the rarity of this type of fungus in the vagina is proved by the fact that of several hundred strains isolated from the vagina in our clinic, only in 4 strains were we able to prove the formation of asci. These 4 strains were isolated from 2 patients. In neither patient were we able to suspect the presence of the fungus from the symptoms of the patient or from the vaginal examination.

Saccharomyces belong to the group of commercially important yeasts and are of no, or at least of minor, importance in medical mycology. Their importance is assumed because of the necessity of differentiation from the nonascosporeogenous *Monilia* and *Cryptococci*.

RESULTS OF THE INTRADERMAL TESTS

Forty-nine of the 100 patients tested showed some degree of reaction to 1 or more of the 5 antigens used.

Of the 49 patients with positive intradermal tests, 15, or 30.6 per cent, were positive by culture for fungi belonging to the genus *Monilia*. In 12 of the 15 patients with positive intradermal tests and cultures, the species of *Monilia* isolated corresponded to the patient's skin tests. In most of these patients, however, positive intradermal tests were obtained with other species of *Monilia*.

Of the 51 patients with negative intradermal tests, *Monilia* were isolated from either the vagina or labia or both in 19, or 37.3 per cent.

TABLE VII. TWENTY-FOUR-HOUR SKIN TEST REACTIONS TO 5 SPECIES OF *MONILIA*

AREA OF ERYTHEMA	ALBICANS	STEL-LATOIDEA	CANDIDA	KRUSEI	PARASILOSIS
Less than 1 cm.	16	19	7	3	3
1 cm.-2 cm.	22	17	4	2	0
2 cm.-3 cm.	7	6	0	0	0
3 cm.-4 cm.	1	2	1	0	0
Totals	46	44	12	5	3

The percentage of patients harboring *Monilia* either in the vagina or on the labia was higher in the group of patients with negative intradermal tests than in the group with positive tests.

The twenty-four-hour skin test reactions are shown in Table VII.

RESULTS OF AGGLUTINATIONS

The results of the agglutinations with the serum titers are shown in Table VIII. Thirty-five of the 100 patients whose sera were tested against the stock strains of the 5 species of *Monilia* showed agglutinins to 1 or more species. The highest and lowest titers recorded were 1:80 and 1:5, respectively.

TABLE VIII. POSITIVE AGGLUTINATION TESTS WITH SERUM TITERS

SERUM DILUTIONS	ALBICANS	STEL-LATOIDEA	CANDIDA	KRUSEI	PARASILOSIS
1:5	7	8	3	0	1
1:10	13	12	15	1	2
1:20	4	7	4	1	0
1:40	1	2	2	0	0
1:80	2	1	0	0	0
Totals	27	30	24	2	3

Of the 35 patients whose sera showed agglutinins, positive cultures for *Monilia* were obtained from 12, or 34.4 per cent.

Of the 65 patients with no agglutinins 22, or 33.8 per cent, were positive by culture for *Monilia*.

The presence or absence of agglutinins in the patient's serum could not be used as an index of vaginal or labial infection.

THE RELATIONSHIP OF THE PRESENCE OF MONILIA AND TRICHOMONADS TO SMEAR TYPE

Monilia were cultured more frequently from patients with Type 2 smears. As was expected the majority of the patients with trichomoniasis showed no Döderlein bacilli by smear and belonged to the Type 3 Group. However, it is interesting to note the occurrence of trichomonads in 9 patients whose smear showed only gram-positive rods of Döderlein's type. This is contrary to the general belief and is in line with recent work by Weinstein,¹⁸ 1938, on the relation of Döderlein's bacillus to vaginal acidity. It is our belief from personal observations, that Neisserian organisms as well as trichomonads occur in a small percentage of patients with smears showing Döderlein's or related bacilli as the only other organisms present. Some doubt is cast on the protective ability of the acidophilus group of vaginal bacilli.

TABLE IX

	TYPE 1 SMEAR 63 PATIENTS		TYPE 2 SMEAR 38 PATIENTS		TYPE 3 SMEAR 99 PATIENTS	
	TRICHO- MONADS	MONILIA	TRICHO- MONADS	MONILIA	TRICHO- MONADS	MONILIA
NO.	9	11	13	15	59	31
%	14.3	17.5	34.2	39.5	59.5	31.3

The smear groupings of the 200 patients, with the incidence of trichomonads and *Monilia*, are shown in Table IX.

THE COMPARISON OF CULTURAL, FRESH PREPARATION, AND SMEAR METHODS OF DETECTION OF YEASTLIKE FUNGI

The use of cultural methods for the detection of yeastlike fungi from the vagina was superior to either the examination of fresh preparations or smears. Sixty-six patients were positive by culture. In 28 of these patients, the fungi were demonstrable by examining fresh preparations and in 23 patients by stained smears. As a general rule in patients with a severe mycotic vulvovaginitis, the fungi can be demonstrated without culture. In carriers or patients with a mild infection, cultures are usually necessary.

DISCUSSION

Obviously little progress can be made in the study of fungus infections of the vulva and vagina until systematic methods of study and classification are adopted. Much of the confusion existing is due to the large number of asymptomatic carriers. Especially is this true of the pregnant female. Furthermore the normal mycologic flora, if such ex-

ists, of the vagina must be established before too much significance can be attached to the findings of unidentified yeastlike fungi by culture. Any evaluation of therapeutic methods of treatment must of necessity be based upon the complete identification of the species of fungus involved as well as the symptoms of the patient.

In interpreting the results of this study, it must be kept in mind that the 200 patients in the series represented the types of individuals usually seen in the outpatient clinic, seeking prenatal care. If the patients had complained previously of pruritus, discharge, or irritation, they were excluded from the series. As a consequence the symptoms in most of the patients were of a mild nature.

The high incidence of trichomonads in the patients with positive cultures for yeastlike organisms often made the interpretation of the patients' histories and vaginal findings difficult from the mycologic standpoint. Although no definite statements can be made as to the relative pathogenicity of the different genera and species, without considering the resistance of the individual and certain predisposing factors such as diabetes, it is interesting that symptoms of otherwise unexplained pruritus were confined to the groups harboring 3 species of *Monilia*: *albicans*, *stellatoidea* and *candida*.

An examination of the tables shows that of the 86 patients with positive cultures for yeastlike fungi the impression of mycotic vulvovaginitis was listed only 16 times; that fresh preparations were positive for yeastlike fungi prior to culture in 28 patients. This would indicate that all patients with unexplained pruritus, regardless of the findings on the vaginal examination, should be cultured for yeastlike organisms.

No explanation is offered for the high incidence of the new species, *Monilia stellatoidea*, in the pregnant group of patients in contrast to the low incidence of this species of *Monilia* in gynecologic patients with a chief complaint of severe mycotic vulvovaginitis (unpublished data). This present report, however, has only confirmed our earlier belief that *M. stellatoidea*, although closely related to *M. albicans*, deserves species recognition.

In the 16 patients with positive cultures for yeastlike organisms, belonging to the genera *Saccharomyces* and *Cryptococcus*, a diagnosis of mycotic infection from the vaginal examination was not recorded. Only 2 of the patients in this group complained of pruritus; one of these patients had trichomonads and *M. albicans* in addition to the *Cryptococcus*, and the second patient had trichomonads. It is doubtful that *Cryptococci* or *Saccharomyces* will produce vaginal or vulval symptoms except under unusual conditions.

Skin tests as a diagnostic measure are of no value. It is our feeling that in the gynecologic or obstetric patient complaining of marked symptoms of mycotic vulvovaginitis, a markedly positive skin test means a marked sensitivity and some relief may be obtained by desensitization. Desensitization, however, does not eradicate the fungus.

Agglutinations are of little significance in mycotic vulvovaginitis. This fact is to be expected because of the high prevalence of *Monilia* in sputum, stools, etc.

An examination of the table, regarding the relation of *Monilia* and trichomonads to the types of bacteria as determined by smear, shows that yeastlike organisms occur in rather high percentages regardless of smear type. Trichomonads occur with greater frequency in patients whose smears show the absence of Döderlein's bacillus or in the Type 3 group. Although none of the patients was diagnosed clinically as trichomoniasis, 9 in the Type 1 group showed trichomonads.

SUMMARY

1. Cultures of yeastlike fungi from the vaginas and vulvas of 200 pregnant women were positive in 86 (or 43 per cent) of the patients. These fungi belonged to the genera *Monilia*, *Saccharomyces*, or *Cryptococcus*. Sixty-six (33 per cent) of the patients showed positive vaginal cultures; 20 (10 per cent) showed positive labial cultures with negative vaginal cultures.

2. A total of 151 strains of yeastlike fungi were classified according to the method previously described by Jones and Martin. Each strain identified as *M. albicans* was pathogenic for rabbits. Each strain identified as *M. stellatoidea* was nonpathogenic for rabbits.

3. In patients in whom the fungi were identified as belonging to the genera *Saccharomyces* or *Cryptococcus*, no symptoms referable to a mycotic infection were described. Symptoms in patients with positive cultures for yeastlike fungi, belonging to the genus *Monilia*, were found only in those in whom the 3 species, *albicans*, *stellatoidea* and (*candida*) *tropicalis* were isolated. Although the incidence of trichomonads was higher in the patients from whom *M. stellatoidea* was cultured, more patients complained of pruritus in the group from which *M. albicans* was cultured.

4. Intradermal skin test with antigens from the 5 species of *Monilia* showed no correlation between positive cultures and positive intradermal tests. The incidence of *Monilia* was higher in the group with negative skin tests.

5. The presence or absence of agglutinins in the patient's serum could not be used as an index of vaginal or labial infection with *Monilia*.

6. Vaginal smear typing showed that monilia were found more frequently in patients with Type 2 smears; that trichomonads were found more frequently in patients with Type 3 smears.

7. Additional work must be done on the mycologic flora of the vulva and vagina in normal patients and in patients with mycotic vulvovaginitis, before we may understand the relative pathogenicity of the different genera and species of yeastlike fungi and may evaluate methods of diagnosis and treatment.

*Since this paper went to press it has been agreed at an informal meeting of medical mycologists attending the Third International Congress for Microbiology, September 2 to 9, 1939 in New York City, to substitute the generic term *Candida* for *Monilia*. Although Berkhout's original description of the genus *Candida* will require mending, it was the consensus of opinion of those present that the existing confusion would be greatly clarified if workers in this field would use only one generic term while awaiting official action by the rules committee of the International Botanical Congress. Consequently the generic term *Monilia* should be *Candida*.

In this present report therefore the correct names for the five species of mycelial-forming, nonascosporeous yeastlike fungi are *Candida albicans*, *Candida stellatoidea*, *Candida tropicalis*, *Candida Krusei* and *Candida parakrusei*.

REFERENCES

- (1) *Castellani, A.*: J. Trop. Med. **23**: 101, 119, 133, 1920. (2) *Schroder, R.*: Centralbl. f. Gynäk. **45**: 1350, 1921. (3) *Castellani, A., and Taylor, F. E.*: J. Obst. & Gynaec. Brit. Emp. **32**: 69, 1925. (4) *Popoff, N. W., Ford, F., and Cadmus, W. H.*: AM. J. OBST. & GYNEC. **18**: 315, 1929. (5) *Plass, E. D., Hesselstine, H. C., and Borts, I. H.*: Ibid. **21**: 320, 1931. (6) *Benham, Rhoda W.*: J. Infect. Dis. **49**: 183, 1931. (7) *Hesselstine, H. C.*: J. A. M. A. **100**: 177, 1933. (8) *Stovall, W. D., and Pessin, S. B.*: Am. J. Clin. Path. **3**: 347, 1933. (9) *Benham, Rhoda W., and Hopkins, Anne McH.*: Arch. Dermat. & Syph. **28**: 532, 1933. (10) *Hesselstine, H. C., Borts, I. H., and Plass, E. D.*: AM. J. OBST. & GYNEC. **27**: 112, 1934. (11) *Hopkins, E. W., and Hesselstine, H. C.*: J. Lab. & Clin. Med. **21**: 1105, 1936. (12) *Hopkins, E. W., and Hesselstine, H. C.*: Ibid. **21**: 1113, 1936. (13) *Carter, Bayard, and Jones, C. P.*: South. M. J. **30**: 294, 1937. (14) *Martin, Donald S., Jones, Claudius, P., Yao, K. F., and Lee, L. E.*: J. Bact. **34**: 99, 1937. (15) *Bland, P. Brooke, Rakoff, A. E., and Pincus, I. J.*: Arch. Dermat. & Syph. **36**: 760, 1937. (16) *Jones, Claudius P., and Martin, Donald, S.*: AM. J. OBST. & GYNEC. **35**: 98, 1938. (17) *Hibbert, G. Fielding, and Falls, Frederick H.*: Ibid. **36**: 219, 1938. (18) *Weinstein, Louis*: Yale J. Biol. & Med. **10**: 247, 1938. (19) *Weinstein, Louis, and Wickerham, Lynferd, J.*: Ibid. **10**: 553, 1938.

DISCUSSION

DR. P. BROOKE BLAND, PHILADELPHIA, PA.—We all have been impressed by the high percentage of yeastlike organisms Dr. Carter and his associates recovered by cultural methods. However, in a study of a large group of patients in our clinic, the findings were strikingly similar. In our investigation, comprising an analysis of the vaginal secretions of 1,200 consecutive patients, we discovered yeastlike fungi in 362, or 31.6 per cent.

One should not, however, make a diagnosis of vaginal mycosis on the basis of a positive culture alone. As has been already indicated, many patients may harbor a few of the organisms in the vaginal tract without exhibiting any symptoms or signs of the disease, even over long periods of observation. When by some alteration in nature's method of fungistasis, environmental conditions become favorable for the propagation of the parasites, clinical phenomena supervene.

For the confirmation of clinical infection, Rakoff prefers wet or Gram stained smears. By this method of investigation he was able to confirm the clinical diagnosis in 181, or 15.1 per cent, of our series of patients. In the great majority of these patients, there were present definite clinical signs of the disease. At this point it might be of some importance to mention that in nonpregnant women, our incidence of positive cultures was only 10 per cent and of clinical infection only 2 per cent.

In his study of the various types of mycobacteria Dr. Carter refers, of course, to the common saccharomyces, and he, I presume, includes the different sub-varieties. In this connection I thought it might be of some interest to mention a form we have frequently met with in our work commonly known as the endomyces, a genus characterized by segmented mycelia. For example, in a study of 327 cultures for the presence of mycelia and asci we found endomyces in 12, or 3.2 per cent. The incidence of the other genera was as follows:

<i>Monilia</i>	332	89.5 per cent
<i>Cryptococcus</i>	20	5.4 per cent
<i>Saccharomyces</i>	6	1.7 per cent

Like most other workers who have attempted the species differentiation of *Monilia*, we have been disappointed in the available methods of study and the results obtained thereby. We are particularly anxious to investigate the new species described as *Monilia stellatoidea*. The low pathogenicity of this strain for rabbits as compared with *Monilia albicans* is noteworthy. In our experience, the pathogenicity of any strain of *Monilia* for rabbits was not definitely related to the pathogenicity of the organisms for human beings, as confirmed by experimental inoculations. It is the vaginal environment, especially the quantity of glycogen present, which appears to be the essential factor.

On the basis of criteria described by Benham, which includes: (1) Morphologic characteristics; (2) growth on various media; (3) carbohydrate fermentation reactions; (4) serologic studies, and (5) pathogenicity, we attempted the identification of 210 strains during the past five years with the following results:

<i>Monilia albicans</i>	143	68.6 per cent
<i>Monilia candida</i>	20	9.5 per cent
<i>Monilia parasitosis</i>	18	8.6 per cent
<i>Monilia krusei</i>	11	5.2 per cent
Unidentified	18	8.6 per cent

We have not been able to satisfy ourselves that species differences according to this method of classification are of clinical significance.

The observations of Dr. Carter and his fellow-workers on the association of trichomonas and monilia emphasizes the importance of always examining fresh, wet smears in addition to stained preparations and cultures. The experienced observer can find almost always both organisms in the wet smear alone. It is also surprising how frequently the presence of a dual infection may be recognized clinically. Where only the fungi are present, the discharge is scanty, quite thick, and of "cottage cheese" or "bread crumb" consistency. The predominant symptom is pruritus. When trichomonads are also present the discharge is more profuse, of a yellowish gray color, and in addition there are small thick masses of "cottage cheese" material suspended in the discharge. The patients complain of both leucorrhea and pruritus.

In our group of patients, the two organisms were found concurrently in 10.4 per cent. On two occasions Vincent's organisms were associated with *Monilia*. In only one instance was the gonococcus associated. Leptothrix occurred in 8.4 per cent of our patients. The presence of leptothrix is mentioned especially because this funguslike organism is not infrequently mistaken by inexperienced workers for the hyphae of monilia.

Döderlein's bacilli were present with *Monilia*, either alone or with other organisms, in 68.2 per cent of the patients. This, we believe, is due probably to the presence of large quantities of glycogen in the vagina during pregnancy and which forms a favorable substratum for both lactobacilli and fungi.

Finally, I should like to inquire whether Dr. Carter and his associates have noted any correlation in the species of *Monilia* in children with oral thrush and the organisms found in the vaginas of infected mothers. Personally, we have been impressed by the high incidence of oral thrush in babies born of infected mothers in the private home where the possibility of contamination from other children is more or less negligible.

DR. A. N. CREADICK, NEW HAVEN, CONN.—In Dr. Weinstein's first published series of 400 cases, 67 yeasts were recovered, and in that series Döderlein's bacillus appeared only with a low pH. Knowing that Dr. Carter was going to discuss this subject, we ran a series of routine cultures on patients presenting themselves to the Gynecological and Obstetrical Dispensary and in a private office, and in 109 cases demonstrated 17 *Monilia*, which we did not differentiate into different strains. There was no correlation between organisms associated with *Monilia*, and there was no correlation of gynecologic conditions and yeasts.

DR. E. D. PLASS, IOWA CITY, IOWA.—I believe as Dr. Creadick pointed out that there must be some change in the physiology of the vagina that makes the *Monilia* pathogenic at times and nonpathogenic at other times. It is well known that both the *Monilia* and the trichomonads may be present without producing symptoms, and we have unpublished evidence that the gonococcus may occasionally be asymptomatic. So the fundamental question concerns the change in the vaginal physiology which suddenly leads to symptomatic manifestations in the course of these infections, or in turn relieves the symptoms of discharge and infection.

As a result of our own independent studies, I completely agree with Dr. Carter that we can obtain very little practical help from either agglutination or skin tests

in cases of moniliasis. We at present are trying to determine whether there may be a local rather than a general sensitivity and are testing the sensitivity of the vaginal mucosa.

There are two practical points I think should be emphasized: One is that the best place to cultivate the *Monilia* is in the middle vagina, where they may have a more acid environment. The second is that the mere determination of the presence of the possible pathogens does not mean that one should limit his therapy to the eradication of that organism.

DR. CARTER (closing).—There have been classified to date 294 vaginal and vulval strains, and we know this classification will stand up under the closest scrutiny. The classification is simple and adequate, and from the classification of the various genera and species, we hope in subsequent work to answer some of the questions concerning response of these infections to various methods of therapy.

We too have tried to find the factor which might explain the difference between the findings in the obstetric patients and the findings in the gynecologic patients. The pH of the vagina has given us much trouble, and we are not satisfied with any method we have tried. At the present time we are working in collaboration with a physicist in an attempt to find an accurate and scientific method of determining the vaginal pH. We, too, have done glycogen stains on biopsy specimens of vaginal mucosa, but have never satisfied ourselves that this glycogen factor might explain the predominance of *Monilia stellatoidea* in the vaginas of the pregnant women. We have injected fungus vaccines into the vaginal mucosa and have biopsied the injected areas to study the type of cellular reaction found. We have cultured the penis of the husband of the patient harboring these *Monilia* in the vaginal canal and rarely can we culture fungus from the penis.

We are still attempting to classify the vaginal streptococci and have met with little success. In our original work on the normal vaginal flora, we found anaerobic streptococci in 48 per cent of the gynecologic patients with normal vaginas, and in 44 per cent of the obstetric patients with normal vaginas. We found gamma streptococci in 39 per cent of the gynecologic patients and in 20 per cent of the obstetric patients; we found alpha streptococci in 9 per cent of the gynecologic patients and 10 per cent of the obstetric patients; we found only 3 strains of beta streptococci in the pregnant series and none in the gynecologic series.

We do find that we can alleviate symptoms by local treatment, but we cannot say that we eradicate the yeastlike fungi from the vulvas or the vaginas. In many patients who show a markedly positive skin test to a vaccine made from the fungi found on their vulvas and in their vaginas, we have found that desensitization by means of the vaccines often leads to a marked improvement of the patient's symptoms. However, we have never been able by vaccine therapy to eradicate the yeastlike fungi from the vulvas or vaginas. We may also state that endocrine therapy has given us no lead as to the possible eradication of yeastlike fungi.

In this report it is interesting to note that symptoms of otherwise unexplained pruritus were confined to the groups harboring 3 species of *Monilia*: *albicans*, *stellatoidea*, and *candida*. Only by careful classification and subsequent accurate follow-up may we increase our knowledge of the various genera and species of the vulval and vaginal fungi and the part these fungi play in producing symptoms. Furthermore it is essential that we know the various genera and species before we may determine the effect of our therapeutic measures.

STUDIES ON THE URINARY TRACT AFTER DELIVERY*

W. T. McCONNELL, M.D., AND LAMAN A. GRAY, M.D., LOUISVILLE, KY.

(From the Department of Obstetrics and Gynecology, University of Louisville Medical School)

THIS study was begun after the occurrence of severe pyelitis in two pregnant patients under our care, followed by slowly diminishing dilatation of the ureters and kidney pelves for nearly two years. This prompted us to inquire when the urinary tract should return to normal after delivery and the variations in such time, and also to study the ureters and kidneys months after an attack of pyelitis of pregnancy. Regarding the first, much could be learned from the literature; but with the latter apparently little work has been done.

There have been many discussions of the dilatation of the ureters and kidney pelves during pregnancy. Several writers¹ have mentioned the early descriptions of Rayer in 1841, and of Cruveilhier in 1843. Opitz in 1905 perhaps first ascribed the dilatation of the urinary tract to pressure from the enlarging uterus. In various early reports of autopsies, dilatations were said to be present in from 25 to 100 per cent of the cases (Carson²). In 1925 Kretschmer and Heaney³ used retrograde pyelography to show dilatation in all of 12 cases of pyelitis and in 16 of 19 normal cases. Since then many studies have been made by means of retrograde and intravenous pyelograms. Duncan and Seng⁴ in 1928 studied 78 apparently normal pregnancies with retrograde pyelography, finding some degree of dilatation in every case, more often and more marked on the right side. These findings have been largely confirmed by many investigators, except that very occasional cases may apparently show no dilatation. An excellent review of the large literature has been recently made by Traut and Kuder.⁵

Several causes of dilatation of the urinary tract have been suggested. The most frequently mentioned cause is that of obstruction of the ureters. The enlarging uterus has been considered by many, particularly the earlier workers, as the prime reason for the dilatation, through its direct pressure effect. The fact that the dilatation is almost always above the pelvic brim involving the upper ureter and kidney pelvis lends weight to this theory, while the ureter below the pelvic brim shows little or no dilatation. The right ureter and pelvis may show marked dilatation; and in the left, none. When the dilatation is bilateral, it is as a rule more marked on the right side. This difference is attributed to the sigmoid which may act as a cushion to protect the left ureter, to the anatomy of the iliac arteries which causes a more marked angle in the crossing of the ureter on the right and to the dextro-rotation of the uterus (also perhaps due to the sigmoid), causing more pressure on the right ureter.

The obstruction-from-pressure theory is refuted by the fact that dilatation occasionally occurs in the second month of pregnancy, although

*Read at the Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 7 to 9, 1939.

usually becoming apparent after the fourth month. Also the dilatation becomes most marked around the seventh month, to recede somewhat before delivery. DeLee felt that since the specific gravity of the uterus is the same as that of the other abdominal organs, pressure from the uterus would be impossible. But Williams considered that the uterus caused direct pressure on the ureters. Several have felt that, since catheters can easily be passed up the ureters, obstruction is not present. It would seem to us that the diffuse pressure external to the ureter might collapse atonic ureters and yet this distributed pressure not be noted by the entering catheter.

Some have stated that similar dilatations do not occur with pelvic tumors of similar size. This, however, is refuted by Baker and Lewis,⁶ who found such dilatations in 16 cases with pelvic tumors. Hundley and others¹ found agreeing dilatations in 7 of 8 cases with pelvic tumors, with rapid regression after operation. While some authors (Lee and Mengert⁷) have stated that the dilatation is not relieved by indwelling catheters for twenty-four hours, Hundley shows photographs of definite decrease in the hydroureters and hydronephrosis after two to three days.

It has also been postulated that in part, the obstruction may be caused by the general hyperemia of the pelvic tissues at the time of pregnancy.

Considering further the obstruction theories, exclusive of pressure from the uterus and general pelvic hyperemia, Hofbauer's⁸ work stands out for its originality. By the examination of 14 autopsy specimens, he demonstrated a definite hypertrophy of the periureteral sheath in the lower ureter near the bladder, consisting of connective tissue and longitudinal muscle fibers. He considered that this hypertrophy and hyperplasia encroached upon the lumen of the lower ureter and was responsible for the urinary obstruction. Several others have confirmed this anatomic finding of Hofbauer's, but are uncertain as to its role in dilatation. Baird⁹ states that the amount of hypertrophy and hyperplasia does not always correspond to the degree of dilatation, and that while the dilatation is more marked on the right side, the hypertrophy is the same in both ureters.

In contrast to the theories of obstruction, there are those who believe that atony of the urinary tract is either wholly or in part responsible for the dilatation. Relaxation and atony of the uterus, large bowel and other pelvic structures are rather evident, and similar atony of the urinary tract would not seem unlikely. Traut and McLane¹⁰ by means of the hydrophorograph have shown that diminished peristaltic activity progresses up to the seventh or eighth month, with some definite return of activity in the last month of pregnancy. They feel that this diminished peristaltic activity cannot be explained on a basis of dilatation, because in a few instances very widely dilated ureters were possessed of normal muscular activity, and because of at least a partial return of peristalsis during the ninth month. It would seem that tracings from hydroureters and hydronephroses not related to pregnancy, but of like duration, should be compared to arrive at an accurate opinion. The work of Traut and McLane is exceedingly interesting, highly suggestive, but not conclusive in our opinion. The increase in tone near delivery has also seemed likely to a number of investigators who found a decrease in dilatation in the ninth month by means of intravenous pyelograms. Many writers have spoken vaguely of hormonal action producing atony of the ureters, while others intimate that this should be a known fact. Hundley and associates were unable to produce any changes in ureters of dogs by estrogenic hormone (amniotin). Recently Brack and Langworthy¹¹ have shown that estrogenic hormone increases the vesical muscle tone in castrated cats. So far as we know, there is no proof that ureteral atony is due to hormonal action.

Our conclusions from the literature of the probable cause of dilatation of the urinary tract in pregnancy are in accord with those of Baird. There is very likely some atony, the cause of which is unknown, possibly

of hormonal origin. Superimposed are the above-mentioned physical factors causing obstruction, the most important of which is pressure from the uterus. There may be some hormonal factor increasing the tone of the upper urinary tract immediately before term.

It is of great importance in the follow-up study of any case of pyelitis of pregnancy to know when the physiologic hydroureter and hydronephrosis return to normal.

Duncan and Seng indicate simply that the majority of their cases returned to normal by the ninth day, but that many had not returned to normal by the twenty-fifth day and that some showed dilatation for a long time. Kretschmer, Heaney, and Ockerly,¹² state that of 32 normal cases, 59 per cent returned to normal after two weeks, 34 per cent after six weeks, and 6 per cent after twelve weeks. Lee and Mengert found a definite reduction in dilatation in six to twenty-four hours after delivery and some normal after the third post-partum day. The majority were said to have been normal by the ninth day. Hundley and associates found that of 26 cases, 8 had returned to normal within one week, 5 after two weeks, 12 after six weeks, and 1 after eight weeks.

PERSONAL OBSERVATIONS

In our own series of supposedly normal cases, there are 12 to be added to the literature (Table I). These were all primiparas. The ages varied from 17 to 22 years. The urinary histories were negative. The urine showed no pus cells. Intravenous pyelograms, using 20 c.c. of Diodrast* without reaction, were made in each case as shown in Table I. Attempts were made in each case to have a picture in the ninth month, but the time varies from one day to eight weeks before delivery. Of the 12 cases before delivery, 9 patients showed hydronephrosis on the right, and 3 on the left. The more marked dilatations were found on the right. Three pelves were found normal on the right, and 9 on the left. Hydroureters were found 3 times on the right, and 8 times on the left. This paradox we do not understand. It was of considerable interest that the left ureter was deviated laterally at the pelvic brim in 9 cases from $1\frac{1}{2}$ to 5 cm., while the right was found deviated in only 2 cases. This latter finding has been mentioned by Hundley. One wonders if it might be related to dextrorotation.

In 10 cases intravenous pyelograms were made in less than ten days after delivery (average seven days). Two of these cases had already returned to normal and had shown moderate or moderately large hydronephrosis before delivery. In the remaining 8 cases there was slight reduction in the dilatation in 2, whereas in 2 others there was very definite increase. Frequently the tortuosity of the ureter in its upper third seemed much more marked in the first week after delivery. Two cases, followed eleven and twelve weeks, showed complete return to normal, but had had only slight hydronephrosis and hydroureter previously. Three cases of the more marked dilatations, followed from seven to fourteen weeks, gave no evidence of return to normal. One patient (Case 7) in this series developed an unclassified toxemia, with drowsiness and swelling of hands. Nonprotein nitrogen was 19. Urine, ++ albumin;

*The Diodrast used in this study was very kindly furnished by the Winthrop Chemical Company.

TABLE I. NORMAL PREGNANCY

CASE	AGE	TIME BEFORE DELIVERY	INTRAVENOUS PYELOGRAM	TIME AFTER DELIVERY	INTRAVENOUS PYELOGRAM
1	18	15 da.	Hydronephrosis, right large	8 da.	Hydronephrosis, right, some larger. Left some larger
				3 mo.	Hydronephrosis, right as before except better cuppings Left pelvis normal
2	20	34 da.	Hydroureter, bilateral, slight	7 wk.	Normal pyeloureterogram
				14 wk.	Hydronephrosis, right, slight (aberrant vessel) Hydroureter, left, slight
3	21	28 da.	Normal pyeloureterogram	5 da.	Hydronephrosis, left, moderate Hydroureter, left, slight, marked tortuosity upper third
				4 wk.	Normal pyeloureterogram
4	20	8 wk.	Hydroureter, left, slight, tortuous	6 da.	Hydroureter, left, slight, somewhat less
				11 wk.	Normal pyeloureterogram
5	22	5 wk.	Hydronephrosis, right moderate Hydroureter, right, slight Hydronephrosis, left very slight	6 da.	Normal pyeloureterogram
				9 wk.	Normal pyeloureterogram
6	17	18 da.	Hydronephrosis, right slight. (Little excretion 25 minutes)	9 da.	Hydronephrosis, right slight Hydroureter, right, slight
				12 wk.	Normal pyelogram (ureters not shown)
7	17	14 da.	Hydronephrosis, right large Hydronephrosis, left, moderately large Hydroureter, left slight (Toxemia unclassified)	3 wk.	Hydronephrosis, right moderately large Hydronephrosis, left, large (more than before delivery) Hydroureter, bilateral moderate
				7 wk.	Hydronephrosis, bilateral almost as before Ureters not shown
8	18	11 da.	Hydronephrosis, right, moderate Hydroureter, left, moderate	7 da.	Hydronephrosis, bilateral, slight Hydroureter, bilateral, marked
9	19	18 da.	Hydronephrosis, right, moderately large Hydroureter, left, slight	8 da.	Hydronephrosis, right, moderate Hydroureter, right, moderate

TABLE I—CONT'D

CASE	AGE	TIME BEFORE DELIVERY	INTRAVENOUS PYELOGRAM	TIME AFTER DELIVERY	INTRAVENOUS PYELOGRAM
10	17	14 da.	Hydronephrosis, right marked Hydronephrosis left, moderate Hydroureter, left, moderate	5 da.	Hydronephrosis, right, slightly less Hydroureter, left, slightly less. (Left kidney normal)
11	22	8 wk.	Hydronephrosis, right, moderately large Hydroureter, left, slight	8 da.	Normal pyelogram
12	18	1 da.	Hydronephrosis right, slight Hydroureter, right, moderate Hydroureter, left, slight	9 da.	Hydronephrosis, right, slight (upper pole) Hydroureter, right, slight

occasional white blood cells. Blood pressure was 150/108 to 130/88. Apparently prompt recovery. It is interesting that this patient had a large hydronephrosis on the right, and moderately large on the left. Seven weeks after delivery there was essentially no change in the pyelograms.

From a consideration of our cases, we do not agree with Lee and Mengert that the majority return to normal by the ninth post-partum day. While it is probably true from the literature that the vast majority of cases return to normal within four to eight weeks and some even within one week, this small series shows three cases with definite abnormalities after seven, twelve, and fourteen weeks. It is even doubtful that these might ever return completely to normal. One (Case 7) of these patients did show some toxemia.

In the literature there are relatively few follow-up studies on women with pyelitis of pregnancy. Corbus and Danforth¹³ in 1927 studied 13 cases from two to four weeks after delivery, finding in every case either hydronephrosis, hydroureter, or ureteral stricture. Hofbauer reported the unpublished work of Gardner and Hoerner on 27 patients after from four to thirty-three months. Nine had had puerperal pyelitis and showed on follow-up examination no dilatation or positive cultures. Of the cases with pyelitis before delivery, 8 (44 per cent) later showed marked dilatation of the ureter. These latter patients had had the more severe symptoms.

Dodds reported 124 cases of pyelitis in which the patients were followed up for a considerable period of time, noting symptoms, urine examinations, and cultures. Apparently few x-ray pictures were made. She concluded that of 84 antenatal cases, 49 per cent were cured (sterile culture), 35 per cent had chronic pyelitis, and 16 per cent had bacteriuria only. Of 40 patients with puerperal pyelitis, 60 per cent were cured, 10 per cent had chronic pyelitis, and 30 per cent bacteriuria only. She concluded the outlook was better in puerperal pyelitis than in antenatal pyelitis. No patient in the series of antenatal cases suffered from an acute pyelitis in a subsequent pregnancy.

Traut and Kuder quote Hazelhorst, who studied 62 women, finding minor difficulties in 39, exacerbations in 19, and hypertension in 3. Also, Robecchi found in patients, five to thirty months after pyelitis, that 23 per cent were normal while 77 per cent showed some degree of hydroureter, albuminuria, pyuria, and bacteriuria.

In our study there are 28 patients who had pyelitis of pregnancy from five months to fourteen years ago. Twenty-one were antenatal

TABLE II. PYELITIS OF PREGNANCY

CASE	AGE	GRAV- IDA	PYELITIS OF		SIDE	FOLLOW-UP SYMPTOMS	TIME SINCE DELIVERY	FOLLOW-UP PYELOGRAM
			PREG.	PUER- PER.				
1	35	i		+	Rt.	Backache	11 mo.	Hydronephrosis, rt., sl. Hydroureter, rt., sl.
2	25	i	+++		Rt.	None	2 yr.	Hydronephrosis, rt., mod. Hydroureter, rt., sl.
3	39	ii	++++		Rt.	None	16 mo.	Tortuosity left ureter
4	32	i	++++		Rt.	None	17 mo.	Hydronephrosis, rt. mod. Hydronephrosis, lt. sl.
5	31	i		++++	Rt.	None	3 yr. 4 mo.	Hydronephrosis, bil. sl. Small stone lt. kidney
6	29	ii	+++		Rt.	None	13 mo.	Hydroureter, rt., sl.
7	25	i	+++		Rt.	Pain rt. side	5 mo.	Normal pyelouretero- gram
8	23	i	+++		Lt.	Nephro- lithotomy	3 yr.	Hydronephrosis, lt., sl. multiple stones Hydroureter, lt., mod.
9	33	ii	+++		Bil.	Persistent pyuria	2 yr.	Hydronephrosis, bil., marked
10	30	ii		++	Rt.	None sl. pus	8 mo.	Hydronephrosis, rt. marked Hydronephrosis, lt. mod. Hydroureter, bil., mod.
11	24	i	++++		Rt.		5 mo.	Hydronephrosis, rt. marked Hydroureter, rt., mod. Hydroureter, lt., sl.
12		i	+++		Bil.	Malaise	1 yr. 5 mo.	Hydronephrosis, rt., sl. Hydroureter, bil., marked
13	25	i	++		Rt.	Backache unrelieved susp. uter.	4 yr.	Hydronephrosis, rt., mod. Hydroureter, lt., mod.
14	27	i	+++		Rt.	Pain rt. side—pul- monary tubercu- losis	1 yr. 8 mo.	Hydronephrosis, rt., mod. Hydroureter, rt., mod.
15	26	i	++++		Rt.	Recurrent pyelitis	1 yr. 8 mo.	Hydronephrosis, rt., mod. Hydroureter, rt., mod.
16	32	vi		++++	Rt.	Backache	6 yr.	Hydronephrosis, rt., mod. Hydroureter, rt., mod.
17	24	i	++++	+	Bil.	None	2 yr. 1 mo.	Tortuosity lt. ureter Poor excretion dye
18	25	iii	+++ 1st		Rt.	None	6 yr.	Sl. tortuosity rt. ureter
19	25	iii		+++ 3rd	Rt.		4 yr.	Hydronephrosis, rt., mod. Hydronephrosis, lt., sl. Hydroureter, bilat., mod.
20	32	iii	++++ 3rd		Bil.	Now preg. 8 mo.	5 yr.	Hydronephrosis, rt., marked Hydronephrosis, lt., mod. Hydroureter, bilat., mod.
21	39	vii		++ 7th	Lt.		5 yr.	Normal pyelouretero- gram

TABLE II—CONT'D

CASE	AGE	GRAV- IDA	PYELITIS OF		SIDE	FOLLOW-UP SYMPTOMS	TIME SINCE DELIVERY	FOLLOW-UP PYELOGRAM
			PREG.	PUER- PER.				
22	30	iii	++++ 2 & 3		Bil.	Pains rt. side—pus		Hydronephrosis, rt., marked Hydronephrosis, lt., sl. Hydroureter, rt., mod.
23	32	iii	+++ 3rd	-- 2nd	Lt.	Pain lt. side persist. pus	3 yr.	Hydronephrosis, rt., mod., fuzzy Hydroureter, bil., mod.
24	20	i	+++	++	Rt.	Persistent pyuria	6 mo.	Hydronephrosis, rt., mod. Hydroureter, lt., sl.
25	24	i	++++		Bil.	Pain rt. side Occ. cystitis	1 yr. 5 mo.	Hydronephrosis, rt., sl. Hydroureter, rt. sl.
26	26	i		++++	Bil.	None	1 yr.	Hydronephrosis, bilat., sl.
27	30	ii	++++ 1st		Bil.	Pain lt. side	12 yr.	Hydronephrosis, rt., mod. Hydronephrosis, lt., sl. Hydroureter, rt., mod. Hydroureter, lt., sl.
28	38	i	++++		Rt.	Frequent cystitis	14 yr.	Tortuosity rt. ureter

and 7 post partum. All but one were of moderate or severe degree. Fourteen were primiparas and 14 multiparas. In 17, the right kidney was apparently solely or mainly involved, 8 were bilateral, and 3 were on the left side.

No records of urinary studies are available on any of the patients before the pyelitis of pregnancy occurred, and we have very few pyelograms made during the pregnancy involved. However, these patients were returned after a considerable period of time as shown in Table II. Intravenous pyelograms were made in 22 cases and retrograde pyelograms in 6 cases.

The abnormal findings were very numerous. Hydronephrosis was present on the right in 20 patients (71 per cent), marked in 5, moderate in 10, and slight in 5. Hydronephrosis was found on the left in 10 patients (35 per cent), marked in 1, moderate in 2, and slight in 7. Hydroureter was present on the right in 15 patients (53 per cent), marked in 1, moderate in 10, and slight in 4. Hydroureter on the left was found in 10 patients (35 per cent), marked in 1, moderate in 6, and slight in 3.

It is of interest that in 3 cases of hydronephrosis on the right side, the ureter arose high on the pelvis such as has been described in cases with an aberrant vessel. If due to a vessel this would apparently be a congenital abnormality, but it is interesting to speculate on the relation of the hydronephrosis of pregnancy to the persistence seen with the aberrant vessel.

Definite tortuosity of the ureter was prominent in 13 patients, on the right side in 9, and on the left in 5.

One patient showed such poor excretion of dye that only a portion of a tortuous left ureter could be seen. In the remainder the excretion was prompt and satisfactory pictures were obtained. This would probably indicate that kidney function in general was not greatly impaired.

In two patients there were stones in the left kidney. Both were found three years after delivery. One had a small asymptomatic stone in the upper calyx, while the other showed multiple large stones recently removed at operation.

In only two patients were apparently normal pyelograms found. One of these has pain and tenderness in the right flank after five months, while the other has no complaints. Fifteen of these patients (53 per cent) at the present time have either backache, pain in the side or persistent pyuria, while the remainder have no complaints, but have not had complete studies.

In contrast to the literature our 7 cases of puerperal pyelitis show changes similar to the whole group. Six patients had hydronephrosis on the right, one marked, 2 moderate, and 3 slight. There were 4 with hydronephrosis on the left, 1 moderate, and 3 slight. Four had hydroureters on the right and 2 on the left. One contained a small stone and 1 pyeloureterogram was normal.

While the above findings are most numerous and appear very serious, the majority of these patients are by no means seriously ill. In some without symptoms and good drainage, we doubt that cystoscopic treatment after thorough investigation is necessary. In these the fibrosis may have been simply enough to destroy elasticity necessary for the return to normal after delivery, but not interfering with drainage. On the other hand, it would seem that in many cystoscopic treatments should have been instituted to eradicate infection and stasis. The general custom has been to dismiss patients after the fever of pyelitis has subsided, hoping that urinary antiseptics and time will result in cure. It is obvious that all patients with pyelitis during pregnancy and the puerperium should be followed by intravenous pyelograms, urine examinations, and bladder cultures as indications for further urologic treatment.

SUMMARY

1. Some degree of dilatation of the ureters and kidney pelves occurs in almost every case of normal pregnancy. This usually regresses to normal in from one to seven weeks after delivery, although apparently it may last much longer in certain cases.

2. Twenty-eight patients who had pyelitis of pregnancy from five months to fourteen years ago have been studied with intravenous or retrograde pyelograms. Twenty-six (93 per cent) showed some degree of abnormality in the x-rays, the more serious changes occurring in 18 (64 per cent).

3. The most frequent findings were hydronephrosis (71 per cent) and hydroureter (53 per cent) on the right side. Stones were present in two cases.

4. This large percentage of abnormalities indicates the necessity of careful urologic studies after pyelitis of pregnancy.

We wish to acknowledge the valuable work of Dr. J. D. Gordinier, who assisted in the preparation of this paper.

REFERENCES

- (1) *Hundley, J. M., Walton, H. S., Hibbitts, J. T., Siegel, I. A., and Brack, C. B.*: AM. J. OBST. & GYNEC. 30: 625, 1935. (2) *Carson, W. J.*: J. Urol. 16: 167, 1926. (3) *Kretschmer, H. L., and Heaney, N. S.*: J. A. M. A. 85: 406, 1925. (4) *Duncan, J. W., and Seng, M. I.*: AM. J. OBST. & GYNEC. 16: 557, 1928. (5) *Traut, H. F., and Kuder, A.*: Internat. Abstr. Surg. 67: 568, 1938. (6) *Baker, E. C., and Lewis, J. S., Jr.*: J. A. M. A. 104: 812, 1935. (7) *Lee, H. P., and Mengert, W. F.*: J. A. M. A. 102: 102, 1934. (8) *Hofbauer, J.*: Bull. Johns Hopkins Hosp. 42: 118, 1928. (9) *Baird, D.*: Lancet 2: 983, 1932. (10) *Traut, H. F., and McLane, C. M.*: Surg. Gynec. Obst. 62: 65, 1936. (11) *Brack, C. B., and Langworthy, O. R.*: Endocrinology 25: 111, 1939. (12) *Kretschmer, H. L.,*

Heaney, N. S., and Ockerly, E. A.: J. A. M. A. 101: 2025, 1933. (13) Corbus, B. C., and Danforth, W. C.: J. Urol. 18: 543, 1927. (14) Dodds, G. H.: J. Obst. & Gynaec. Brit. Emp. 39: 46, 1932.

DISCUSSION

DR. ROBERT A. ROSS, DURHAM, N. C.—This study re-emphasizes the necessity for a careful and prolonged follow-up of the urinary tract after infections and operative procedures which may leave a scar on this system which may later be translated in terms of frequency of urination, infection, obstruction, stone formation, and arterial kidney damage.

When one considers the anatomy of the ureter and its similarity to other smooth muscle of the gastrointestinal and genitourinary tracts, and when one recalls the proved effect of the sex steroids and pituitary substance on such muscle, it is perfectly orderly to ascribe a great many alterations to these factors. Occasionally we find the effect to be of benefit, as in the patient with stricture who became pregnant.

We have been interested particularly in the study of urinary infection in relationship to the toxemias of pregnancy, because the toxemia of pregnancy is our major obstetric complication. Our findings are in accord with the abstracted material from Dr. Mussey's paper. Pyelitis and urinary infection occur most often in our private patient group, toxemia in our clinic group. Private patients constitute only one-fourth of the admissions on our obstetric service, yet 60 per cent of the patients admitted for pyelitis are in this group. Twenty-five per cent of all obstetric admissions have some degree of toxemia as a complication, and 5 per cent of these have convulsive eclampsia. Yet again the urinary infection is not predominantly in this group.

Our follow-up would lead us to agree with the authors' figures as to the time elapse before a return to normal, as would other observations of the post-partum woman. It is more likely to be six weeks or six months, rather than one to six weeks, before the female organism is again normal.

DR. FREDERICK H. FALLS, CHICAGO, ILL.—There are three points that I would like to make in connection with a discussion of these two last papers. The first is that physiologically there is a change in the lower end of the ureter during pregnancy. That change is a hypertrophy of the sheath of Waldeyer which tends to close or constrict, or form more of a sphincter at the lower end of the ureter than is normally present in the nonpregnant woman.

The second point is that the uterus and the urinary tract arise from the same embryologic *anlage*, and to me it is quite impossible to conceive of a mechanism that has been provided to prevent the uterus from emptying itself, without it affecting the mechanism for the extrusion of urine. It has been observed that in pregnant women, especially those with pyelitis, the urinary peristalsis, as estimated by watching the extrusion of dye from the urinary meatus by cystoscopic examination, is much slower on the normal side as compared with the normal patient, and on the affected side as compared with the normal side of the affected woman. Now the normal mechanism for the retention of the fetus in the uterus is hormone, and progesterone is an antipituitrin. This peculiar recovery that occurs must, it seems to me, be due at least in part to the action of progesterone on the ureter, helping possibly by stasis to prevent increasing the likelihood of infection ascending from the bladder and producing pyelitis.

Another reference I would like to make is to the pathology that is present in the ureters of women who have had pyelitis. It was my misfortune to have a patient die of post-partum hemorrhage which was due to a severe anemia produced by the pyelitis. Anemia associated with pyelitis has not been sufficiently appreciated. A study of the urinary tract will show us why Dr. McConnell finds these changes persisting over some months. Probably the ureter never returns to normal after having suffered a serious pyelitis change.

DR. GRAY (closing).—It seems likely that progesterone will be the hormone found to cause dilatation of the ureter. It is now possible to obtain progesterone in large doses and certainly such a hormone should be studied on normal dogs or other animals.

These patients should not be dismissed by the obstetrician as soon as the temperature becomes normal and the condition regresses, but they should first have the benefit of the new treatment for pyelitis, that is sulfanilamide, mandelic acid, or sulfapyridine, the latter particularly for staphylococcus infections. If this were done for six weeks, during the time the ureter is trying to return to normal, possibly such results as we have found would not again occur.

IS THERE A CLINICAL RELATIONSHIP BETWEEN PYELITIS OF PREGNANCY AND PRE-ECLAMPTIC TOXEMIA?*

ROBERT D. MUSSEY, M.D., AND SIM B. LOVELADY, M.D., ROCHESTER, MINN.
(From the Section on Obstetrics and Gynecology of the Mayo Clinic)

INTEREST in the possible relationship between pyelitis and the toxemias of pregnancy has been given renewed impetus by the work of Peters and his co-workers,¹⁰⁻¹² and others, on the role of pyelitis in the production of the toxemias of pregnancy.

Peters called attention to the fact that no convincing evidence of the causative factors of toxemias has been demonstrated and asserted that the syndrome designated toxemia has been wrongly named. He stated that toxemia, apart from pyelitis, should not be considered an entity. Calling attention to the prevalence of ureteral dilatation among pregnant women, he indicated that this condition is common among patients with toxemia, some of whom had not had a history of renal infection or other infection at the time the toxic symptoms began. Peters admitted that "hypertension usually appears only after pyelonephritis has persisted for a long time and has destroyed a large part of both kidneys." He stated also that women who have pyelitis when pregnant seldom escape irreparable and enduring damage if the pregnancy is allowed to proceed. Reviewing 320 cases of toxemia of pregnancy, Peters and his co-workers noted that 41, or 13 per cent, of the patients suffered at one time or another from pyelitis or pyelonephritis. Among 93 patients with pyelitis complicating pregnancy, these authors noted that 25 had hypertension or edema or both before pregnancy was terminated.

After studying 100 cases of pyelonephritis in nonpregnant individuals subjected to necropsy Weiss and Parker, Jr.¹⁶ concluded that chronic pyelonephritis results in the gradual diminution of kidney structure, "contracted kidney," and in decreased function; that patients who had pyelonephritis in early childhood showed a marked tendency for a certain type of toxemia of pregnancy to develop. Weiss estimated that pyelonephritis is responsible for 15 to 20 per cent of the total number of cases of malignant hypertension. In contrast to these findings, Acosta-Sison reported evidence of pyelonephritis in only one among 38 cases in which death from eclampsia was followed by necropsy.

Hayes reported 20 cases in which pre-eclamptic toxemia was cured by ureteral drainage employed to relieve back pressure on the kidneys, which he postulated as the cause of toxemia. La Vake, Talbot, Johnston, Johnson and Nicholas and others have stated that the acute toxemias are produced by toxic products from the placenta damaged by infection from foci. On the contrary, Theobald observed the almost complete absence of eclampsia in Siam, where infection of the urinary tract is prevalent. Baird noted that patients with marked ureteral stasis with or without urinary infection have a normal or low blood pressure and are not subject to "albuminuria of pregnancy." He found that pyelitis seldom develops in women in whom albuminuria and a rise in blood pressure develop

*Read at the Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 7 to 9, 1939.

during pregnancy and in the very few cases in which urinary infection has been observed it has been transitory. Baird stated that these patients are more susceptible to pyelitis of the puerperium. Herriek agreed that pyelitis of pregnancy is a fairly common complication, but usually exists apart from any manifestations of so-called toxemia, and McLane stated that there is no proved relationship between pyelitis and the toxemias of pregnancy.

The writings of various observers indicate a difference of opinion concerning the incidence of pyelitis. Baird reported that 20 per cent of the women admitted to the antenatal wards of a London hospital during their first pregnancy had pyelitis; these patients comprised more than one-third of all patients admitted with pyelitis of pregnancy. In contrast to this high incidence are the low percentages reported by other authors: Traut, 2 per cent; Crabtree 2.5 per cent among 4,662 deliveries; Cabot, quoting members of the Boston Obstetrical Society, 0.7 per cent; and recently, McLane, 1.2 per cent among 14,000 deliveries. One hundred and seventeen patients with a positive diagnosis of pyelitis of pregnancy were observed at the Mayo Clinic during the years 1924 to 1937, inclusive; during this period there were 5,960 deliveries, an incidence of pyelitis of practically 2 per cent. This ratio of approximately two cases of pyelitis among one hundred pregnant women is similar to that of most of the reports previously cited. This review indicates also that pyelitis occurs more frequently in the first than in subsequent pregnancies.

At the outset of this discussion of the possible relationship between pyelitis of pregnancy and pre-eclamptic toxemia, it should be made clear that we are using the generally accepted term, toxemia, as a part of the name for the acute hypertensive syndrome of late pregnancy commonly called pre-eclamptic toxemia; by its use we do not intend to affirm or deny hypotheses that the syndrome of pre-eclamptic and eclamptic toxemia is necessarily due to a toxin or toxins.

There remains considerable confusion concerning an acceptable classification of the toxemias of pregnancy. In order to clarify our use in this paper of the terms, pre-eclampsia and eclampsia, we are including the following classification of the toxemias of pregnancy agreed upon by a subcommittee of *The American Committee on Maternal Welfare*: vomiting of pregnancy, pre-eclampsia, eclampsia, renal disease, hypertensive disease, and an unclassified group. Possibly acute yellow atrophy of the liver should be included; this and vomiting of pregnancy may be disregarded in this discussion. The acute hypertensive toxemias of late pregnancy (the third trimester) are pre-eclampsia and eclampsia, whose entire syndrome has developed in the course of a given pregnancy; in this respect the acute toxemias are distinct from cardiovascular-renal conditions with which the woman was affected prior to pregnancy and which are prone to exhibit symptoms of exacerbation earlier in pregnancy than the third trimester. Complete discussion of the unclassified group is not pertinent to this paper. In it are placed cases whose symptoms and findings do not permit of definite diagnosis and classification; for example, sometimes it is impossible to differentiate between acute pre-eclamptic toxemia and certain cases of mild antecedent vascular disease with superimposed toxemia.

The terms ureteritis, pyelitis, and pyelonephritis need no explanation. Since it is frequently impractical or impossible to determine during pregnancy the extent of involvement of the urinary tract in cases of acute infection, the term, pyelitis, is used in this paper to indicate inflammation of any or all portions of the upper urinary tract.

In order to determine the possible clinical relationship between pyelitis of pregnancy and pre-eclamptic toxemia, the case histories of pregnancies complicated by either one or both of these diseases have been scrutinized. The case histories of patients with pyelitis of pregnancy and of the puerperium have been examined to ascertain whether acute toxemia developed (1) during the course of pregnancies complicated by pyelitis or (2) in subsequent pregnancies occurring under our supervision. The case histories of all certain cases of acute late toxemia of pregnancy were examined to determine (1) how many of these patients had pyelitis antecedent to pregnancy and (2) in how many evidence of pyelitis developed during the puerperium.

This review embraced the study of histories of 117 proved cases of pyelitis complicating pregnancy and 163 cases of acute hypertensive toxemia of late pregnancy seen at the Mayo Clinic between Jan. 1, 1924, and Dec. 31, 1937, inclusive. Only cases of pre-eclampsia and eclampsia are included in the toxemic group and in each case the history or examination must have furnished sufficient data to determine the presence or absence of complicating pyelitis. The number of cases in the acute hypertensive group is relatively small because cases of doubtful diagnosis or those with evidence of antecedent vascular or nephritic disease, except possible pyelitis or pyelonephritis, were discarded. The diagnosis of all cases of pyelitis is based on the presence of pus and often red cells in catheterized urine, fever, usually chills and often symptoms such as pain along the urinary tract, urinary disturbance and physical findings of costovertebral and abdominal tenderness. In practically all cases observed during the later years of this review the infecting organism was determined by culture of the urine. Among those patients observed early in this series a large majority were examined cystoscopically, and in 42, or 36 per cent, of the entire series the diagnosis was confirmed in this manner.

Among the 117 patients with pyelitis, in 92 the disease occurred in the course of pregnancy and in 25 in the puerperium. In the case of 3 patients, pyelitis of pregnancy was followed or accompanied by the development of acute toxemia. A fourth patient (Case 4) with fulminating pyelonephritis died with acute renal failure probably associated with cortical abscesses; necropsy was not obtained, and it is debatable whether this case should be classed as a true pre-eclamptic toxemia.

REPORT OF CASES OF PYELITIS OF PREGNANCY THAT PRECEDED THE APPEARANCE OF PRE-ECLAMPTIC TOXEMIA

CASE 1.—The patient had severe bilateral pyelonephritis at three and one-half months after the beginning of her first pregnancy. Pre-eclamptic toxemia developed during the eighth month and she still had pus Graded 4, on a basis of 1 to 4, in the urine. She had four subsequent pregnancies and even though she showed evidence of a mild degree of chronic nephritis there was no flare-up of acute toxemia or pyelitis. This is the only case in this series in which evidence was obtained of residual kidney damage with lowered renal function following pyelitis of pregnancy.

CASE 2.—The patient had an attack of pyelitis during the fourth month of her first pregnancy. She carried to term and delivered a normal baby. In the course of her fifth pregnancy, pre-eclamptic toxemia developed.

CASE 3.—The patient had 2 normal pregnancies. During the fourth month of her third pregnancy she had a severe attack of pyelitis which responded to treatment. She had 5 subsequent normal pregnancies; during the ninth pregnancy she had a severe grade of acute toxemia which necessitated interrupting the pregnancy.

CASE 4.—The patient had an attack of bilateral pyelitis in the eighth month of her first pregnancy and was extremely ill with high temperature when referred to us ten days later. The disease did not respond to treatment, including the use of indwelling ureteral catheters. Following spontaneous onset of labor she delivered on the fourth day after admission. After a septic course she died on the twelfth day post partum from renal insufficiency (nonprotein nitrogen 171), probably with renal cortical abscesses; necropsy was not obtained.

Thirty women who had pyelitis of pregnancy were under our care during one or more subsequent pregnancies without showing evidence of recurring pyelitis; in 2 cases (Cases 2 and 3) noted in the preceding paragraphs, evidence of toxemia developed in a subsequent pregnancy. It is of interest that acute toxemia did not develop among 10 patients, each of whom had an attack of pyelitis either prior to or in the course of pregnancy and one or more subsequent attacks of pyelitis in the course of ensuing pregnancies.

REPORT OF CASES WITH HISTORY OF TWO OR MORE ATTACKS OF PYELITIS IN WHICH TOXEMIA DID NOT DEVELOP

CASE 5.—The patient had had recurring attacks of pyelitis for three years previous to her first pregnancy. She had an attack during this pregnancy but no signs of toxemia.

CASE 6.—The patient had an attack of pyelitis two years prior to her first pregnancy and an attack during the sixth month of gestation. She showed no signs of toxemia during this pregnancy nor in one subsequent pregnancy of which we have record.

CASE 7.—The patient had pyelitis prior to her second pregnancy and an attack of pyelitis during this pregnancy. She had 3 subsequent pregnancies without toxemia.

CASE 8.—The patient had pyelitis prior to her second pregnancy, and during the sixth month of this pregnancy. She had two subsequent pregnancies without toxemia even though signs and symptoms of pyelonephritis persisted after delivery of her fourth baby.

CASE 9.—The patient had pyelitis previous to her second pregnancy and an attack during the sixth month. She had one subsequent pregnancy without toxemia.

CASE 10.—The patient had an attack of pyelitis with her first pregnancy and an attack during the eighth month of her second pregnancy. She had 2 subsequent pregnancies without toxemia.

CASE 11.—The patient had pyelitis five years prior to her first pregnancy, and an attack during the sixth month of this pregnancy. There were no signs of toxemia.

CASE 12.—The patient had an attack of pyelitis with her first pregnancy and during the last month of her second pregnancy; there were no signs of toxemia.

CASE 13.—The patient had a left nephrectomy prior to her first pregnancy. An attack of right pyelitis developed during the sixth month of gestation but there were no signs of toxemia.

CASE 14.—The patient had previous acute pyelonephritis and left ureterolithotomy. She had repeated attacks of pyelitis during her fourth pregnancy but revealed no signs of toxemia.

None of the 163 patients with pre-eclamptic toxemia gave a history of pyelitis prior to the first pregnancy; in 6 cases pyelitis developed during the puerperium.

REPORT OF CASES OF ACUTE TOXEMIA IN WHICH PYELITIS LATER DEVELOPED

CASE 15.—The patient was referred to us with eclampsia. Symptoms of pyelitis developed on the third day of the puerperium.

CASE 16.—The patient suffered from rather severe pre-eclamptic toxemia during her first pregnancy. Two days post partum she had the onset of pyelitis.

CASE 17.—The patient had a mild toxemia with her first pregnancy and pyelitis developed three days post partum.

CASE 18.—The patient had mild toxemia with her first pregnancy and pyelitis developed two days post partum.

CASE 19.—The patient had post-partum pyelitis following her first pregnancy in which she had had pre-eclamptic toxemia.

CASE 20.—The patient had 5 normal pregnancies. During the sixth pregnancy she had pre-eclamptic toxemia. Two months after her eighth child was born she had an attack of acute cystitis and pyelitis. She had 2 subsequent normal pregnancies.

COMMENT

The publications of Peters and his co-workers and others on pyelitis and pyelonephritis have given renewed impetus to the interest among obstetricians in the possible relationship between pyelitis and the toxemias of pregnancy. Pyelitis may be of sufficient severity and duration to damage the kidney structure and curtail renal function. Pregnant women with lowered renal function caused by severe pyelitis are subjected to increased hazard as well as are those with lowered function resulting from other renal diseases or from generalized vascular disease. Hypertension is the predominant finding in the acute toxemias of late pregnancy; it is rarely present in cases of acute pyelitis or pyelonephritis. Acute systemic arteriolar changes of a spastic nature have been reported by many observers among many cases of pre-eclamptic toxemia and eclampsia, but rarely have such changes been found in cases of acute pyelitis. Our clinical data indicate that acute pyelitis of pregnancy is rarely either the indirect or direct cause of acute hypertensive toxemias which arise in the course of pregnancy.

Among 117 cases of pyelitis of pregnancy, acute hypertensive toxemia developed in three and a fatal inflammatory kidney lesion developed in a fourth. Among 163 patients with pre-eclamptic toxemia or eclampsia, 6 showed symptoms of pyelitis in the puerperium; none gave a history of pyelitis prior to the first pregnancy. The 2 per cent incidence of pyelitis among this group of pregnant women appears to correspond with the findings of the majority of other observers. When treatment was instituted early a large majority of these cases of pyelitis responded with reasonable promptness to the usual medical methods of treatment so that in recent years the necessity for urologic consultation has been infrequent.

It has been said that any woman who has had vascular or renal disease, including pyelitis, should not be allowed to proceed with pregnancy. This statement is too inclusive as patients with such conditions should be individualized. Women with undoubted renal disease should be advised against subsequent pregnancy. Some recover from acute renal disease and in others the residual damage is so mild as to escape the usual methods of examination. Among this group of patients with pyelitis, 30 were carried through one or more subsequent pregnancies; in 2 cases of the 4 previously mentioned, toxemia developed in a subsequent pregnancy.

The results among the cases here reported would indicate that acute pyelitis of pregnancy when treated promptly is not prone to cause pre-eclamptic toxemia or eclampsia, and that following one attack of acute pyelitis of pregnancy the majority of such women do not exhibit symptoms of residual renal damage.

REFERENCES

- (1) *Acosta-Sison, H.*: AM. J. OBST. & GYNEC. 22: 35, 1931. (2) *Baird, D.*: J. Obst. & Gynaec. Brit. Emp. 43: 1, 1936. (3) *Cabot, Hugh*: Modern Urology in Original Contributions by American Authors, Philadelphia, 1936, Lea & Febiger 2: p. 540. (4) *Crabtree, E. G.*: Quoted by Cabot, Hugh.³ (5) *Hayes, B. A.*: Urol. & Cutan. Rev. 40: 545, 1936. (6) *Herrick, W. W.*: Discussion, Tr. A. Am. Physicians 51: 293, 1936. (7) *Johnston, R. A., Johnson, H. W., and Nicholas, H. O.*: Texas State J. Med. 25: 515, 1929. (8) *La Vake, R. T.*: Journal-Lancet 36: 600, 1916. (9) *McLane, C. M.*: AM. J. OBST. & GYNEC. 36: 117, 1939. (10) *Peters, J. P.*: J. A. M. A. 110: 329, 1938. (11) *Peters, J. P., Laviates, P. H., and Zimmerman, H. M.*: AM. J. OBST. & GYNEC. 32: 911, 1936. (12) *Peters, J. P., and Zimmerman, H. M.*: Tr. A. Am. Physicians 51: 287, 1936. (13) *Talbot, J. E.*: J. A. M. A. 74: 874, 1920. (14) *Theobald, G. W.*: Lancet 1: 1030, 1930. (15) *Traut, H. F.*: Am. J. Surg. 35: 273, 1937. (16) *Weiss, S., and Parker, F., Jr.*: Tr. A. Am. Physicians 53: 60, 1938.

DISCUSSION

DR. R. T. LAVAKE, MINNEAPOLIS, MINN.—I have made a study of the urinary findings of all pyelitis and late toxemia cases, occurring on the Obstetric Service at the Minneapolis General Hospital during the past ten years. In a total of 15,740 admissions (14,653 deliveries), there were 63 diagnoses of pyelitis unassociated with late toxemia. There were 373 cases of late toxemia. According to the criteria for diagnosis used by Dr. Mussey, the incidence of pyelitis in these toxemic patients was 3.22 per cent. By the most stringent standard of normality for urinary findings set by the laboratory, according to their technique, 72.85 per cent were absolutely normal. This left a group containing 23.93 per cent of the cases of toxemia in which, upon urinary findings alone, one might diagnose varying degrees of urinary infection. There was no correlation between the presence, intensity, or absence of urinary infection, and the presence, intensity, or absence of toxemia.

Time, and the elusive character of general hospital material, made it impossible to determine how many of the cases of pyelitis, unassociated with toxemia during their hospitalization, later developed toxemia. Dr. Mussey's material shows a percentage of 3.26 per cent. This is a most important figure because it gives us an approximate figure of the limits within which pyelitis is likely to operate as a mechanism, if our belief is correct that it can so operate.

Laying aside figures and entering the realm of theory founded upon personal clinical observation and research, I would expect pyelitis to be but an infrequent mechanism in the causation of toxemia. In the first place, infection is only one possible cause of infarction, and clinical findings suggest that it does not always infarct the placenta; and, in the second place, when it does lead to infarction, it is my belief that toxemia will manifest itself only if the products of conception

are toxic to the mother and in degrees varying with degrees of toxicity of the products of conception. If the products of conception are not toxic to the mother, no amount of infarction will cause true late toxemia, although progressive absorption of the dead products may give signs in the mother such as would occur if she were absorbing her own dead tissue. To my mind, pyelitis may be a direct cause of toxemia by infarction of the placenta and an indirect cause by lowering excretory efficiency.

DR. H. W. JOHNSON, HOUSTON, TEXAS.—It may be that further study will enable us to divide our cases of pyelitis into subgroups, and the men in the north may see the kind that we sometimes see in the south, namely, pyelitis accompanied by bleeding, especially from the uterus and cervix.

In four autopsies at our hospital, on deaths from eclampsia, occurring nine days after the convulsions, 3 were complicated by pyelonephritis and 1 by acute miliary tuberculosis. It was hard to say in those cases how much could be attributed to the pyelonephritis or to the tuberculosis.

DR. MUSSEY (closing).—It would be a very interesting thing if others would review their clinical records of patients who have had pyelitis of pregnancy and those with toxemia, and perhaps develop a combined report.

I wondered whether the bleeding Dr. Johnson spoke of might not be due to streptococic pyelitis. We have noticed that where there had been a streptococic infection in association with pyelitis there has been a little tendency to bleed.

Another point which has become evident to us and to the urologists associated with our group is that the urologist is not called in consultation on these cases of pyelitis as often as he used to be. Some ten or more years ago the urologist was called in consultation immediately, and it was taken for granted that the accepted treatment was ureteral catheterization. Gradually it has become evident that if the disease is diagnosed early and treated promptly, ureteral catheterization is rarely necessary.

RATIONALE FOR THE USE OF TESTOSTERONE PROPIONATE IN THE IMMEDIATE TREATMENT OF EXCESSIVE UTERINE BLEEDING*

A. ROBERT ABARBANEL, A.B., M.D., NEW YORK, N. Y.

INTRODUCTION

EXCESSIVE uterine bleeding, next to dysmenorrhea, is the most common disorder of menstruation. Therapeutic trials for relief, with chorionic gonadotropin (pregnancy urine extracts), corpus luteum extracts, and progesterone revealed that their effectiveness was limited.¹ In the search for a more potent agent, investigators have recently presented what promises to be a very effective weapon in controlling excessive uterine bleeding. This substance is the so-called "male" sex hormone, testosterone, most commonly used as its propionic acid ester, testosterone propionate. This report presents a consideration of certain properties of this hormone, noting especially its dual gynecogenic properties. In particular, the two-fold action of testosterone upon the myometrial elements is correlated with certain anatomic and physiologic evidence concerning the uterine circulation at the time of menstruation. On this basis, a reasonably clear working hypothesis has been developed along physiodynamic lines to explain the *modus operandi* by which testosterone may control excessive uterine bleeding. Clinical studies on parenteral and oral therapy, and subcutaneous implantation of pellets of testosterone propionate are discussed.

I. TESTOSTERONE IS NOT ONLY A POWERFUL ANDROGEN BUT ALSO A VERY POTENT GYNECOGEN

One of the most important contributions to our knowledge of sexual physiology has been the recognition of the fact that all of the sexual hormones possess bisexual properties. Each possesses, to a different extent, both androgenic and gynecogenic activity.

For the purpose of both simplifying and clarifying nomenclature, the following scheme of terminology has been adopted:

All of the sexual hormones are definitely bisexual in their action. Where the action is exerted in the direction of "maleness," the term *androgenic* is used. Where the action is exerted in the direction of "femaleness," the term *gynecogenic* is used.

Androgen: A collective term for all substances which are able to restore, to some extent, the male genital tract following castration atrophy, or stimulate its growth directly; or induce or maintain, or both, the secondary sex characteristics of the male.

*Awarded the Foundation Prize for 1939 by the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons.

Presented at the Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., September 7 to 9, 1939, and at a meeting of the Brooklyn Gynecological Society, Brooklyn, N. Y., on November 3, 1939.

The clinical studies were carried out in the Departments of Gynecology of the Johns Hopkins Hospital and the Sinai Hospital, Baltimore, Maryland.

The experimental studies were performed in the laboratories of Dr. Carl G. Hartman at the Carnegie Institute of Anatomy and Embryology, Baltimore, Maryland.

Gynecogen: A collective term for all substances which are able to restore, to some extent, the female genital tract following castration atrophy, or stimulate its growth directly; or induce or maintain, or both, the secondary sex characteristics of the female.

This group is subdivided into two groups of substances: *estrogens* and *progestogens*.

Estrogen: "A collective term for all substances producing an estrous (proliferative) growth in vagina, uterus, and mammary glands and female secondary sex characteristics."*

Progestogen: A collective term for all substances which have the property of producing progestational changes in the female genital tract. (It has become necessary to introduce this term since it has been found that *progesterone*, the pure hormone of the corpus luteum, is not specific in this respect. The term *progestin* refers to impure extracts of the corpus luteum containing a substance having the properties of progesterone.)

Significant, too, are the bisexual potentialities of the gonad, especially in the female, both on an embryologic and biologic basis;^{2, 3} thus it is not surprising to learn that normal ovaries implanted in castrate males may maintain their secondary sexual organs.⁴ Moreover, it has been demonstrated that normal human females may excrete as much androgenic substance in their urine as do normal men.⁵ On the other hand, bull's testes (per weight) and stallion's urine (per volume) are among the richest known sources of estrogenic substances.⁶

The bisexual nature of the sexual hormones is well exemplified by testosterone. In Table I is presented a short outline summary of some of these properties of testosterone compared with those of estrone and progesterone. Study of the data offered reveals that the gynecogenic activity of testosterone is dual, for it may act like an estrogen or a progestogen.

The concept of neutralization of estrogens by testosterone cannot be accepted as a mathematical plus-minus equation. The evidence presented in Table I clearly demonstrates that, in the main, estrone, and testosterone exert a cooperative synergistic action on the female genital tract when given in physiologic amounts. Rather than neutralize, testosterone merely modifies the actions of estrogens. In this respect testosterone may act like progesterone. This would result in an increased excretion of estrogens, as well as cause a shift in the estradiol-estrone-estriol equilibrium to the right.^{63, 64} An increased excretion of estrogens following the administration of testosterone has been observed.^{65, 66}

In short, after surveying the evidence, one may as rightfully call testosterone a "female" sex hormone as a "male" sex hormone.

II. THE MYOMETRIAL ELEMENTS PLAY AN ESSENTIAL ROLE IN CONTROLLING THE VOLUME OF BLOOD FLOWING TO THE ENDOMETRIUM, AND THUS, THE AMOUNT OF UTERINE BLEEDING. THE TWOFOLD ACTION OF TESTOSTERONE UPON THESE MYOMETRIAL ELEMENTS IS SUCH THAT EXCESSIVE UTERINE BLEEDING IS CONTROLLED

The mode of action by which testosterone propionate is able to check uterine bleeding will not be explained fully until it is first known what

*Allen, E.: Sex and Internal Secretions, ed. 2, Baltimore, 1939, Williams and Wilkins Co., p. 453.

factors initiate, what forces maintain, and what combination of circumstances stop the menstrual flow. However, there have recently appeared several excellent anatomic investigations on the menstruating human⁶⁷ and monkey^{68, 69} uteri. Based on these as well as certain studies on the effect of various sex hormones on the circulation in the uterus of the monkey, and, keeping in mind certain physiologic properties of testosterone, a reasonably clear working hypothesis has been developed on a physiodynamic basis.

Well established, indeed, is the fact that uterine bleeding (exclusive of neoplasms and pregnancy) may proceed from every known type of endometrium (proliferative, secretory, hyperplastic, atrophic, or inflammatory). The only common denominator to all of these is the recurrent vascular phenomena in the spiral arterioles. In brief, *menstruation is fundamentally a vascular phenomenon*.

The spiral arterioles arise from the arcuate branches of the uterine artery in the middle third of the myometrium, wind inward, become radial in their course through the inner fourth of the myometrium, and finally extend toward the endometrial surface. Most of them do not give off any branches in the endometrium. They are definitely under hormonal control, for, following castration, these vessels atrophy.⁶⁹ Throughout the menstrual cycle these vessels proliferate with the endometrium. Since they grow more rapidly than the uterine mucosa, they become more and more tortuous, until, premenstrually, they assume a more or less spiral shape, whence their name.⁶⁸ The vessels supplying the deep portion of the endometrium, the basalis, do not undergo cyclical changes.^{68, 69}

Immediately preceding menstruation, these spiral arterioles alternately constrict and dilate, giving rise to the so-called blush and blanch phenomenon.⁷⁰ Then the peripheral portion of these arterioles dilates, one by one, in widely disseminated portions of the mucosa, and at varying intervals, extravasation of blood occurs, which, combined with retrograde flow from the venous capillary bed, appears externally as menstruation. This is soon followed by a marked reduction in the circulation to the area in the mucosa from which extravasation occurred, produced by vasoconstriction of the arteriole supplying that area.

Where does this functional vasoconstriction occur? From a study of the arterioles in the uterine mucous membrane at the time of menstruation, Bartelmez concludes that, because of the extremely great variability found in them, the explanation for the reduction or stoppage of the flow of blood to the mucosa must be sought for in the myometrium and not in the endometrium.⁶⁷

Let us examine the evidence for such possibilities in the myometrium. The spiral arterioles possess an intimate relationship with the myometrial elements. In the monkey, as these vessels pass through the inner fourth of the myometrium, there are distinguishable closely about them bands of specialized muscle tissue, which Daron⁶⁸ has called "contraction cones." In the human being, Bueura⁷¹ has described longitudinal groups of muscle fibers, or "Polster," immediately beneath the tunica intima of the arteries in the female genital tract. These Polster of

TABLE I. COMPARISON OF SOME EFFECTS OF TESTOSTERONE WITH THOSE OF ESTRONE AND PROGESTERONE, ILLUSTRATING SOME OF THEIR BISEXUAL PROPERTIES AS WELL AS THE DUAL GYNECOGENIC PROPERTIES OF TESTOSTERONE

	RESPONSE TO PROGESTERONE	RESPONSE TO TESTOSTERONE	RESPONSE TO ESTRONE
<i>(Castrate not primed with estrogen)</i>			
Uterus Endometrium	Proliferative and progestational ⁷ Monkey, rabbit, rat	I. Proliferative ^{8, 9} Monkey, guinea pig II. Proliferative and progesta- tional ¹⁰⁻¹² Cat, rat, rabbit	Proliferative ¹³ Human being, mon- key, et alia
Myometrium Growth	Slight ^{7, 14} Monkey, rat, rabbit	Marked ^{10, 11} Rat, cat, rabbit	Marked ^{10, 13} Human being, mon- key, et alia
Rhythmic motility	None ¹⁵ Rabbit		Induced ¹⁵ Human being, mon- key, et alia
Tubal motility			Induced ^{15, 16} Human being, rabbit
Vagina	Slight proliferation and mucifica- tion ^{7, 13} Rat	Marked growth, proliferation and incomplete muci- fication ¹⁰ Rat	I. Marked growth, proliferation, strati- fication and cornifi- cation ^{10, 13} Human being, mon- key, rat, et alia II. Mucification (sub- threshold doses) ¹⁷ Rat
Breast	Apparently none ¹⁸ Rat	Slight duct prolif- eration and lobular growth ^{18, 19} Rat	Duct prolifera- tion ^{18, 19} Rat, human being, monkey, et alia
<i>(Castrate primed with estrogen)</i>			
Uterus Endometrium	I. Proliferative and progesta- tional ^{7, 13} Human being, monkey, et alia II. Hypoplasia (chronic experi- ments) ^{7, 20} Monkey, rabbit	I. Proliferative and progesta- tional ^{10-12, 22} Cat, rat, rabbit II. Hypoplasia (chronic experi- ments) ^{23, 24} Monkey, rabbit III. Prolifera- tive ^{8, 21} Monkey	I. Proliferative ¹³ Human being, mon- key, et alia II. Hypoplasia (chronic experi- ments) ^{25, 26} Monkey, rabbit
Myometrium Growth	Moderate ^{7, 14} Monkey, rabbit, et alia	Marked ¹⁰⁻¹² Rat, cat, rabbit	
Rhythmic motility	Inhibition ¹⁵ Human being, rab- bit, et alia	Inhibition ^{22, 27, 28} Human being, rabbit	Inhibition (chronic experiments) ²⁶ Rabbit

	RESPONSE TO PROGESTERONE	RESPONSE TO TESTOSTERONE	RESPONSE TO ESTRONE
Tubal motility	Inhibition ^{15, 16, 29} Human being, rabbit	Inhibition ^{30, 31} Rabbit, human being	Inhibition (chronic experiments) ^{30, 32} Human being
Vagina	Mucification ^{7, 10, 13} Rat, mouse	Marked growth and mucification ¹⁰ Rat	
Breast	Lobulation ¹⁸ Monkey, rabbit, et alia	Incomplete lobulation ¹⁸ Rat	
Ovulation	I. Inhibition ³³ Rat, rabbit II. Stimulation ³⁴ Toad	I. Inhibition ^{23, 35} Human being, monkey, et alia II. Stimulation ^{34, 36} Rat, mouse, toad	I. Inhibition ³⁷ Monkey, rat, et alia II. Stimulation ³⁸ Rat
Menstruation	Inhibition ^{7, 39} Monkey	Inhibition ^{23, 24} Human being, monkey	Inhibition ^{40, 41} Human being, monkey
Pregnancy Ovaries intact	Prolonged ⁴²	Prolonged ⁴³	Prolonged ⁴⁴
Ovaries removed	Rabbit Maintained ⁴⁵ Rabbit	Rat Maintained ⁴⁶ Rat	Rabbit Not maintained ⁴⁵ Rabbit, rat
Lactation	No inhibition ⁴⁷ Rat	I. Partial inhibition ⁴⁷ Rat II. No inhibition if baby continues to nurse ²⁷ Human being	I. Inhibition ⁴⁷ Human being (?), rat, et alia II. No inhibition if baby continues to nurse ⁴⁸ Human being
Gonadotropic factor (Ant. pituitary)	Depressed ^{33, 49} Rabbit, human being	Depressed ^{50, 51} Rat, human being, et alia	Depressed ^{37, 51} Rat, human being, et alia
Corpus luteum (life of)	Apparently prolonged ⁵² Rat	Prolonged ^{52, 53} Rat	Maintained and prolonged ^{54, 55} Rat, rabbit
Vagina (immature rat)	Slight ⁷	Premature opening and slight mucosal proliferation ⁵⁶	Premature opening and proliferation of mucosa ¹³
Spermatogenesis (hypophysectomized rats)	Maintained ⁵⁷	Maintained ⁵⁷	
Prostate (castrate)	Restoration of mucosa toward normal ^{58, 59} Rat	Restoration of mucosa to normal ⁵⁹ Monkey, dog, rat	Growth and squamous metaplasia ⁵⁹ Dog, rat, et alia
Testicular descent		Stimulation ^{48, 60} Human being, monkey, et alia	Inhibition ⁶¹ Rat
Penis (immature)	Hastened growth ⁴⁸ Rat	Hastened growth ^{60, 62} Human being, monkey, et alia	Partial inhibition ⁶² Rat, mouse

(Only key references are given.)

Bucura have been found especially abundant in the inner fourth of the myometrium and in the stratum vasculare. Keiffer has demonstrated that the fibers of the tunica media of these arteries are continuous with the intrinsic muscle fibers of the myometrium.⁷² Further, Okkels and Engle⁶⁹ in the macaque, and Keiffer⁷² and Durante⁷³ in the human being, have described a peculiar sphincter-like arrangement of myometrial fibers about the large vessels in the stratum vasculare. Here bundles of muscle fibers, forming S-shaped loops, interweave with the tunica media of adjacent arteries and veins. In short, the intimate association between the blood vessels and the muscle fibers in the myometrium is such that adequate contraction of the muscular elements would very markedly diminish the flow of blood to the endometrium. The analogy to the bleeding post-partum atonic uterus, and the effects of oxytocics on it, is obvious.

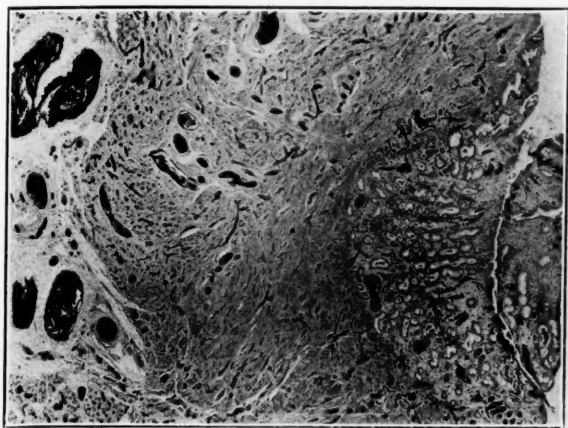
Important, too, in connection with the vascular physiology of the uterus is its rhythmic intermittent contractility, initiated and maintained by estrogens. Immediately before and during menstruation there is a gradual rise in the estrogens in the blood and urine.^{74, 75} This rise is much more likely to be pronounced in cases with functional uterine bleeding.^{6, 64, 74, 76} The human uterus has been found to be actively contracting just before and during menstruation.⁷⁷ Intermittent rhythmic contractility serves to increase the volume flow of blood through the dilated endometrial vessels, because of the pumping action of the movements.⁷⁸ This increase follows the initial hyperemic effect of the estrogens.¹⁵

It now becomes clear that excessive uterine bleeding will occur if the proximal (myometrial) portion of the spiral arterioles fails to constrict, or be constricted, following the initial extravasation of blood distally. Therefore, regardless of the precipitating factor, be it myomas, subinvolution, pelvic inflammatory disease, or merely "functional," one of the basic causes for excessive uterine bleeding is a disruption of the normal hemodynamics of the uterine circulation at the time of menstruation, aided and abetted by a disturbance in the normal pattern of uterine contractility at the same time.

Let us now turn our attention to the physiologic properties of testosterone propionate. From study of Table I, it is noted that the effect of this hormone upon the endometrium is variable. The status of the endometrium, however, is practically unimportant as regards uterine bleeding. In contrast, the response of the myometrial elements is clear-cut and far more significant. The effects of testosterone are twofold. First, this hormone will inhibit the estrogen-induced rhythmic contractility of the uterus.^{22, 28} As a result, the volume flow of blood to the uterus will be decidedly diminished,⁷⁸ for the activity of muscle and its blood supply are, within limits, directly proportional.⁷⁹

In addition, testosterone exerts a direct stimulative action upon the myometrial elements.¹⁰ Inhibition of intermittent uterine contractions is not accompanied by a true relaxation, but merely by a decrease in tension.³⁰ Grossly, the uteri of rabbits and rats, especially after chronic injections of testosterone propionate, appear shrunken.^{48, 80} Biopsies

Myometrium

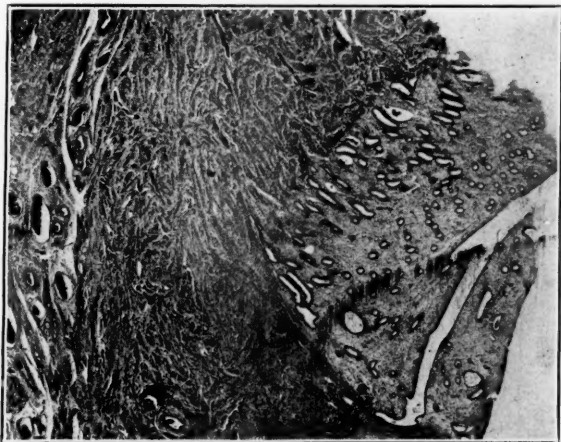


Endometrium

Fig. 1.—Section through uterus of Monkey 604. ($\times 15$.) This animal was castrated and then primed with estradiol di-propionate. Injections of the latter were continued, and at the same time, 1 mg. of crystalline progesterone in oil was given daily for twenty days. The animal was then gassed and the arterial system injected with a suspension of India ink. The blood vessels appear as dark black areas on the photomicrograph.

The rich vascularity of both the myometrium and endometrium is easily visualized. In the endometrium, spiral arterioles may be clearly outlined about the glands. In particular, the inner fourth of the myometrium, where the "contraction cones" of Daron are situated, is very vascular.

Myometrium



Endometrium

Fig. 2.—Section through the uterus of Monkey 606. ($\times 15$.) This animal was castrated and then primed with estradiol di-propionate. Injections of the latter were continued, and at the same time, 1 mg. of crystalline progesterone in oil was given daily for ten days and then 25 mg. of crystalline testosterone propionate in oil daily for the next ten days. The animal was then gassed and the arterial system similarly injected with a suspension of India ink. The blood vessels appear as dark black areas on the photomicrograph.

In contrast to Fig. 1, the uterus here is definitely much less vascular. The stratum vasculare is not reduced in population but in the size of the vessels. The most marked changes, however, have occurred in the inner fourth of the myometrium and the endometrium, whose vascularity is very decidedly decreased.

of these uteri in the intact treated animal are practically bloodless, whereas those from normal untreated animals bleed freely.^{48, 50} Moreover, in the human being, the actively contracting puerperal uterus, experienced by the patient as "after-pains," can be quieted with testosterone propionate.²⁷ At first, the contractions can be felt to diminish in amplitude and somewhat in frequency. At the same time, the uterus can be felt to become firmer and firmer.

Further proof of the direct action of testosterone upon the myometrial elements is offered by the following experimental data. In Fig. 1 is seen a section through the uterus of a castrate monkey who, primed and then maintained with estradiol dipropionate, had been given 1 mg. of crystalline progesterone in oil daily for twenty days. The arterial system was then injected with India ink. The dark black areas represent the blood vessels in the uterus. It is evident on first glance that this organ is very vascular. The large dilated endometrial vessels are clearly outlined. Fig. 2 reveals the uterus of a castrate monkey, similarly primed and maintained, who had received 1 mg. of crystalline progesterone in oil daily for ten days and then 25 mg. of testosterone propionate in oil daily for ten days more. (This dosage was derived from the data of Klein and Parkes¹² who state that the progestational response in rabbits to testosterone propionate is about one-twentieth that of progesterone.) She, also, was injected with India ink. Study of Fig. 2 reveals that the stratum vasculare is not reduced in the density of its vascular population, but in the size of its vessels. It is clearly evident, however, that there has resulted a very marked diminution in the endometrial circulation.

Summing up the evidence, the following conclusions concerning the effect of testosterone upon the myometrial elements appear valid. The volume flow of blood *to* the uterus is definitely reduced by the inhibition of intermittent uterine contractions by testosterone. The volume flow of blood *in* the myometrium, especially in its inner fourth, is decidedly diminished by the direct stimulative action of testosterone upon the myometrial elements, bringing about a functional constriction of the myometrial vessels. The significance of the close anatomic interrelationship between the blood vessels and the muscle fibers of the myometrium now becomes manifest. (A possible added direct action upon the myometrial vessels themselves, however, is not excluded.) Clearly, then, the net result of the twofold action of testosterone upon the myometrial elements will be a marked reduction in the volume flow of blood *to* the endometrium. It follows, therefore, that there will occur a consequent decided decrease in the amount of uterine bleeding. Thus, on a physiodynamic basis, is presented a reasonably clear and logical rationale for the use of testosterone propionate in the immediate treatment of excessive uterine bleeding.

III. CLINICAL STUDIES

Twenty-five patients with excessive uterine bleeding were treated. Their ages ranged from 15 to 49 years. Endometrial studies showed cystic hyperplasia 14 times, an interval non-secretory phase 10 times,

a secretory phase 5 times, and a chronic endometritis once. This makes a total of 30, for 5 of these patients over the course of several years had shown a different type of endometrial picture on separate occasions of excessive bleeding. Two disclosed hyperplasia on one occasion and an interval, non-secretory phase on another. Two were found to have a secretory endometrium and an interval, non-secretory one on separate occasions. One patient had a secretory phase once and endometrial hyperplasia on two subsequent studies. Thus, further evidence is adduced to show that the endometrial status at the time of bleeding is minor. The only factor that was constant in every case was the myometrium. Logically, therefore, it is to the myometrium that we must look for the factors controlling the amount of uterine bleeding.

Dosage, route, and interval of administration will be discussed in detail elsewhere.^{81, 82} Briefly recapitulated, it was found that dosages of 10 to 30 mg. of testosterone propionate would lessen the bleeding materially, while a total dosage of 10 to 120 mg., with a general average of 40 to 60 mg., was necessary to stop the bleeding completely. The initial injection of 10 to 25 mg. of testosterone propionate was given intramuscularly, or else divided between the intramuscular and subcutaneous routes. Subsequent injections, at intervals of two to four days, were given deep subcutaneously in the deltoid region. A therapeutic result was usually obvious in one to four days. Frequently, following a slight initial reduction in flow, an exacerbation of flow may occur. This is transient, usually lasting from three to twelve hours or more. It is practically pathognomonic of a sharp subsequent decrease and rapid cessation of flow. Injections of testosterone propionate should not be given during this temporary increase of flow, for the bleeding may be prolonged over a still longer period of time.

Since spontaneous remission of menorrhagia very frequently occurs, attempts at prophylactic treatment have almost all been confined to the treatment of one or two cycles. If a secretory phase is found premenstrually, from 10 to 30 mg. given in divided *subcutaneous* doses in the seven to ten days before the period will usually be sufficient to control the tendency to excessive flow. If hyperplasia exists, from 50 to 100 mg. given in divided *subcutaneous* doses in the two or three weeks before the expected period will usually suffice.

Two other methods of administration of testosterone propionate were used. These were the oral administration of the hormone (10 mg. tablets) combined with bile salts and the subcutaneous implantation of pellets of crystalline testosterone propionate as a prophylactic measure.

No signs of masculinization were ever noted. In fact, in a personally observed series of over 200 women treated with testosterone propionate for various conditions, no such signs were ever observed. The only possible sign of defeminization was the loss of libido in three patients. It is interesting to note in this connection that nymphomania may be relieved with testosterone propionate.⁴⁸

The following case history will illustrate the oral administration of testosterone propionate plus bile salts as well as the use of pellets of crystalline testosterone propionate.

CASE 1.—A white housewife, aged 30 years, gravida v, para v, came to the dispensary complaining of prolonged, profuse, and painful periods, accompanied by many clots, lasting ten to fourteen days, and saturating an average of 60 double-sized pads per period. Menses began at eleven, recurred at twenty-four to twenty-eight-day intervals, and lasted seven days, always being very profuse. In 1937 right

kidney and ureter were removed for hydronephrosis and ureteral calculi. In 1938 hysterotomy and sterilization were carried out at three months' gestation. Following this procedure, patient developed severe premenstrual cramps which began twelve to fourteen days before onset of flow and continued through most of the period. The flow itself gradually increased until it lasted ten to fourteen days. Pelvic findings were normal.

Beginning the seventeenth day of the next cycle, 10 mg. of testosterone propionate, combined with a bile salt tablet, were given orally each day. Menses began on the thirty-first day. She experienced no premenstrual cramps at all, but had a few at the onset of flow with passage of clots. Flow was profuse for three days and then began to slacken. In order to note whether an increase in flow would result, she was given 10 mg. of testosterone propionate, plus a bile salt tablet, orally. Flow increased several hours later and then began to decrease. The same procedure was repeated two days later with similar results. In review, 10 mg. per day prevented severe premenstrual cramps and dysmenorrhea. Although the flow lasted nine days, it was fairly profuse for only three days, instead of the customary eight to ten days. On the eleventh day of the next cycle (two days after flow ceased), 3 pellets of crystalline testosterone propionate, totaling 25.8 mg., were implanted subcutaneously. (Previous experience indicated that oral therapy gave but temporary results in these cases.) Her next period began on the thirty-first day of the cycle and lasted five days, the flow being fairly profuse on the first two days. She had some mild premenstrual cramps starting a few days before the flow. The following period lasted four days, being profuse for two days. Premenstrual cramps were extremely mild. At present, she is still under observation.

SUMMARY

All of the sexual hormones possess bisexual properties to varying degrees. Testosterone, in particular, is not only a powerful androgen, but also a very potent gynecogen. As regards the female, the effects exerted by testosterone are dual, for it may behave as an estrogen or a progestogen.

A physiodynamic explanation is offered of the *modus operandi* by which excessive uterine bleeding is controlled by testosterone propionate. This interpretation is based, in main, upon the response of the myometrial elements to testosterone propionate.

Substantial anatomic evidence is presented to show clearly that the close structural interrelationship between the blood vessels and the muscle fibers of the myometrium is such that adequate contraction of the myometrium will bring about a functional constriction of these vessels, especially the proximal (myometrial) portion of the spiral arterioles. Consequently, the volume of blood flowing to the endometrium, and thus, the amount of uterine bleeding, will be decidedly decreased.

The essential role played by the myometrial elements in controlling the amount of uterine bleeding now becomes manifest. It follows, then, that excessive uterine bleeding will occur if the proximal (myometrial) portion of the spiral arterioles fails to constrict, or be constricted, following the initial extravasation of blood distally. A basic cause, therefore, for excessive bleeding, regardless of the precipitating factor, be it myomas, subinvolution, pelvic inflammatory disease, or merely "functional," is a disruption in the normal hemodynamics of the uterine circulation accompanied by a disturbance in the pattern of uterine contractility at the time of menstruation.

The response of the myometrial elements to testosterone propionate is twofold. First, this hormone will inhibit rhythmic, intermittent

uterine contractions, thereby eliminating the pumping action of these movements. As a result, the volume of blood flowing *to*, and thus *through*, the uterus will definitely decrease, for the degree of activity of muscle and its blood supply are directly proportional. Second, the direct stimulative, squeezing effect of testosterone upon the myometrial elements will bring about a functional constriction of the myometrial vessels. The sum total of the twofold effects of testosterone propionate (inhibition of intermittent uterine contractions, direct stimulative action upon the myometrial elements) acting simultaneously upon the myometrial elements will result in a decided reduction in the flow of blood *to* the endometrium. Consequently, the amount of uterine bleeding will be very considerably diminished. Upon these considerations, the use of testosterone propionate for the immediate treatment of excessive uterine bleeding finds its rationale.

ACKNOWLEDGEMENTS

I gratefully acknowledge my indebtedness to the following men for their sincere interest and valuable suggestions in carrying out experimental and clinical studies, and in preparation of the manuscript: Dr. Carl G. Hartman of the Carnegie Institute of Anatomy and Embryology; Drs. Emil Novak and Richard W. Te Linde of the Department of Gynecology, Johns Hopkins Hospital; Drs. H. David Silberman and H. Melvin Radman of the Department of Gynecology, Sinai Hospital; and Dr. Samuel R. M. Reynolds of the Department of Physiology, Long Island College of Medicine.

The testosterone propionate and the estradiol dipropionate were supplied under the trade names of "PERANDREN-Ciba" and "DI-OVOCYLIN-Ciba," respectively, by Ciba Pharmaceutical Products, Inc.

The progesterone was supplied under the trade name of "PROLUTON-Schering" by the Schering Corp.

The bile salt tablets were supplied by Hynson, Westcott and Dunning and Riedel-Haen.

The pellets of crystalline testosterone propionate were prepared by Dr. Gerson Biskind of the Department of Pathology, Johns Hopkins Hospital.

REFERENCES

- (1) Jeffcoate, T. N. A.: J. Obst. & Gynaec. Brit. Emp. **44**: 31, 1937. (2) Willier, B. H.: In Allen, E.: Sex and Internal Secretions, ed. 2, Baltimore, 1939, Williams and Wilkins Co., Chap. III, pp. 64-144. (3) Meyer, R.: AM. J. OBST. & GYNEC. **22**: 697, 1931. (4) Hill, R. T., and Strong, M. T.: Endocrinology **21**: 495, 1937. (5) Gallagher, T. F., Peterson, D. H., Dorfman, R. I., Kenyon, A. T., and Koch, F. C.: J. Clin. Investigation **16**: 695, 1937. (6) Zondek, B.: Die Hormone des Ovariums und des Hypophysenvorder Lappens, ed. 2, Vienna, 1935, Julius Springer. (7) Hisaw, F. L., Greep, R. O., and Fevold, H. L.: Proc. Soc. Exper. Biol. & Med. **36**: 840, 1937; Am. J. Anat. **61**: 483, 1937. (8) Hartman, C. G.: Personal communication. (9) Phelps, D., Burch, J. C., and Ellison, E. T.: Endocrinology **23**: 458, 1939. (10) Korenchevsky, V., and Hall, K.: J. Path. Bact. **45**: 681, 1937. (11) Courier, R., and Gros, G.: Compt. rend. Soc. de Biol. **128**: 194, 1938. (12) Klein, M., and Parkes, A. S.: Proc. Roy. Soc., Ser. B **121**: 574, 1937. (13) Allen, E., Hisaw, F. L., and Gardner, W. U.: In Allen, E.: Sex and Internal Secretions, ed. 2, Baltimore, 1939, Williams and Wilkins Co., Chap. VIII, pp. 452-629. (14) Crandall, W.: Anat. Rec. **70**: (Suppl. 3) 18, 1938. (15) Reynolds, S. R. M.: Physiol. Rev. **17**: 304, 1937. (16) Rubin, I. C.: AM. J. OBST. & GYNEC. **37**: 394, 1939. (17) Meyer, R. K., and Allen, W. M.: Anat. Rec. **56**: 321, 1933. (18) Astwood, E. B., Geschickter, C. F., and Rausch, E. O.: Am. J. Anat. **61**: 373, 1937. (19) Turner, C. W.: In Allen, E.: Sex and Internal Secretions, ed. 2, Baltimore, 1939, Williams and Wilkins, Chap. XI, pp. 740-806. (20) Allen, W. M.: Symposia on Quant. Biol. **5**: 66, 1937. (21) Engle, E. T., and Smith, P. E.: Endocrinology **25**: 1, 1939. (22) Robson, J. M.: Quart. J. Exper. Med. **26**: 355, 1937. (23) Zuckerman, S.: Lancet **2**: 676, 1937. (24) Gaines, J. A., Salmon, U. J., and Geist, S. H.: Proc. Soc. Exper. Biol. & Med. **38**: 779, 1938. (25) Engle, E. T., and Smith, P. E.: Anat. Rec. **61**: 471, 1935. (26) Reynolds, S. R. M.: Anat. Rec. **62**: 269, 1935. (27) Abarbanel, A. E.: AM. J. OBST. & GYNEC. **39**: 1043, 1939. (28) Leonard, S. L., Sager, V., and Hamilton, J. B.: Proc. Soc. Exper. Biol. & Med. **37**: 362, 1937. (29) Geist, S. H., Salmon, U. J., and Mintz, M. E.: AM. J. OBST. & GYNEC. **36**: 67, 1938. (30) Rubin, I. C.: Personal communication. (31) Salmon, U. J., Geist, S. H., and Walter, R. I.: AM.

- J. OBST. & GYNEC. 38: 264, 1939. (32) *Cella, C., and Georgescu, I. D.*: Arch. f. Gynäk. 165: 36, 1937. (33) *Makepiece, A. W., Weinstein, G. L., and Friedman, M. H.*: Am. J. Physiol. 119: 512, 1937. (34) *Zwarenstein, H.*: Nature 139: 112, 1937. (35) *Boling, J. L., and Hamilton, J. B.*: Anat. Rec. 73: 1, 1939. (36) *Salmon, U. J.*: Proc. Soc. Exper. Biol. & Med. 38: 352, 1938. (37) *Moore, C. R., and Price, D.*: Am. J. Anat. 50: 13, 1932. (38) *Höhlweg, W., and Chamorro, A.*: Klin. Wehnschr. 16: 196, 1937. (39) *Weisbader, H., Engle, E. T., and Smith, P. E.*: AM. J. OBST. & GYNEC. 32: 1039, 1936. (40) *Foss, G. L.*: Brit. M. J. 2: 10, 1937. (41) *Hisaw, F. L., and Greep, R. O.*: Endocrinology 23: 1, 1938. (42) *Koff, A. K., and Davis, M. E.*: AM. J. OBST. & GYNEC. 34: 26, 1937. (43) *Hamilton, J. B., and Wolfe, J. L.*: Anat. Rec. 70: 433, 1938. (44) *Heckel, J. P., and Allen, W. M.*: Endocrinology 24: 137, 1939. (45) *Idem*: Am. J. Physiol. 119: 330, 1937. (46) *Scipiadès, E.*: Proc. Soc. Exper. Biol. & Med. 37: 242, 1937. (47) *Folley, S. J., and Kon, S. K.*: Proc. Roy. Soc. Med., Ser. B 124: 476, 1938. (48) *Abarbanel, A. R.*: Unpublished data. (49) *Laroche, G., Simonnet, H., and Bompard, E.*: Compt. rend. Soc. de Biol. 126: 1159, 1937. (50) *Salmon, U. J.*: Proc. Soc. Exper. Biol. & Med. 37: 488, 1937. (51) *Wolfe, J. M., and Hamilton, J. B.*: Endocrinology 21: 603, 1937. (52) *McKeown, T., and Zuckerman, S.*: Proc. Roy. Soc., Ser. B 124: 362, 1937. (53) *Wolfe, J. M., and Hamilton, J. B.*: Proc. Soc. Exper. Biol. & Med. 37: 189, 1937. (54) *Robson, J. M.*: J. Physiol. 90: 435, 1937. (55) *Westman, A.*: Arch. f. Gynäk. 158: 476, 1937. (56) *Nathanson, I. T., Franseen, C. C., and Sweeney, A. R.*: Proc. Soc. Exper. Biol. & Med. 39: 385, 1938. (57) *Nelson, W. O., and Merkel, C.*: Proc. Soc. Exper. Biol. & Med. 36: 825, 1937. (58) *Lamar, J. K.*: Anat. Rec. 70: 45 (Suppl. 1), 1936. (59) *Buhler, F.*: Ztschr. ges. Exper. Med. 104: 249, 1938. (60) *Hamilton, J. B.*: Am. J. Physiol. 119: 325, 1937. (61) *Golding, G. T., and Ramirez, F. T.*: Endocrinology 12: 804, 1928. (62) *Raynaud, A., and Lacassagne, A.*: Comp. rend. Soc. de Biol. 126: 868, 1937. (63) *Pincus, G.*: Symposia on Quant. Biol. 5: 44, 1937. (64) *Smith, G. V. S., and Smith, O. W.*: AM. J. OBST. & GYNEC. 36: 769, 1938. (65) *Steinach, E., and Kun, H.*: Lancet 1: 845, 1937. (66) *Dorfman, J. I., and Hamilton, J. B.*: J. Clin. Investigation 17: 67, 1939. (67) *Bartelmez, G. W.*: Carnegie Inst. Wash., Pub. No. 443; Contrib. to Embryol. (No. 142) 24: 141, 1933. (68) *Daron, G. H.*: Am. J. Anat. 58: 349, 1936. (69) *Okkels, H., and Engle, E. T.*: Acta. path. et microbiol. Scandinav. 15: 150, 1938. (70) *Markee, J. E.*: Anat. Rec. (Suppl.) 55: 66, 1933. (71) *Bucura, C. L.*: Zentralbl. f. Gynäk. 34: 561, 1910. (72) *Keiffer, H.*: Bull. Acad. Roy. de Med. de Belgique 13: 253, 1933. (73) *Durante, G.*: Presse méd. 41: 2664, 1933. (74) *Frank, R. T.*: The Female Sex Hormones, Springfield, Illinois, 1929, Charles C. Thomas. (75) *Yerby, L. D.*: Proc. Soc. Exper. Biol. & Med. 36: 496, 1937. (76) *Fluhmann, C. F.*: Disorders of Menstruation, Philadelphia, 1939, W. B. Saunders Co. (77) *Reynolds, S. R. M.*: Physiology of the Uterus, New York, 1939, Paul B. Hoeber, Inc., Chapters I and VI. (78) *Fagin, J., and Reynolds, S. R. M.*: Am. J. Physiol. 117: 86, 1936. (79) *Anrep, G. V.*: Harvey Lectures 30: 146, Baltimore, 1934-35, Williams and Wilkins Co. (80) *David, A.*: Personal communication. (81) *Sturgis, W., Abarbanel, A. R., and Nader, D. N.*: AM. J. OBST. & GYNEC. (In press.) (82) *Abarbanel, A. R.*: AM. J. OBST. & GYNEC. (In press.)

MORRISANIA HOSPITAL

DISCUSSION

DR. WILLIAM H. VOGT, ST. LOUIS, MO.—Recently I had under my care a case of functional bleeding that could not be controlled. This woman then went to another physician and he advised the use of testosterone. The physician who advised this treatment wrote me that he had never seen any masculinization from the use of testosterone. I finally, however, gave it to the patient and she grew a nice little moustache very promptly.

DR. ABARBANEL.—We have not seen any signs of masculinization. This covers a personally observed series of over 225 patients treated for various obstetric and gynecologic disorders. I have seen two patients treated by other men in which masculinization was produced with doses of over 1,000 mg. But this dosage goes back to the pharmacologic discussion as to what constitutes a physiologic dose. One does not have to give huge doses to achieve therapeutic results.

Regarding the moustache Dr. Vogt talks about, it must be remembered that 95 per cent of normal women have some hair on their upper lip. Dr. Vogt would not hesitate to give progesterone, yet this hormone is definitely androgenic. It will produce precocious descent of the testes, hasten the growth of the penis in the immature rat, as well as bring about a marked increase in the size of a guinea pig's clitoris.

STEREOROENTGENOGRAPHY OF 400 PELVES WITH CLINICAL CORRELATION*

JOHN G. WALSH, M.D., PROVIDENCE, R. I.

MANY methods of roentgen pelvimetry which give accurate measurements of the internal diameters of the pelvic inlet have been perfected in the past few years. In skilled hands they have been of great value in estimating disproportion between the fetal head and the inlet, but most methods of pelvic radiography have been disappointing to the clinician, seeking a way to solve the problems of difficult labor and disproportion below the level of the inlet. Although techniques have been greatly simplified, they have never received widespread use in clinical obstetrics. The studies of Caldwell and Moloy¹ on the variations in shape and size of the female pelvis have stimulated renewed interest in pelvic roentgenography in the hope that more frequent prognostication of dystocia may result from the use of the technique they propose. Caldwell and Moloy have classified the pelvis in 5 types, the gynecoid, the android, the anthropoid, the platypelloid and the asymmetrical. In each type distinctive anatomic features in the posterior segment of the inlet, in the sacrosciatic notch and in the subpubic arch are present together with varying degrees of convergence of the side walls and variations in the inclination of the sacrum, which influence the shape and size of the pelvic inlet and outlet. In 1933 Moloy² perfected a method of viewing films through a specially constructed precision stereoscope. Stereoroentgenograms of the inlet, a lateral view of the sacrosciatic notch and a view of the subpubic arch are necessary for a complete study when this technique is employed. The inlet stereoroentgenograms viewed through the stereoscope reproduce a phantom image of the pelvis, reveal its configuration, and make direct measurements of any pelvic diameter possible. Employing this method Caldwell, Moloy and D'Esopo³ were able to estimate the frequency with which each pelvic type occurred and to show that a mixture of the primary types was frequent, the posterior segment of the pelvic inlet of one type being associated with the anterior segment of another type, and also to show from measurements that they may occur in large, average, or small size.

In an effort to determine where in the bony pelvis dystocia occurred and the types of pelvis in which it did occur, the technique proposed by Moloy was used to study the pelvis in 400 women at the Providence Lying-In Hospital. Since the incidence of dystocia in ward cases was low, a selected group occurring in the course of 8,873 deliveries between March 1, 1936, and March 1, 1939, was chosen for study. One hundred multigravida having a history of difficult labor in previous deliveries, and 300 primigravida who, from clinical examination, might

*Read at the Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 7 to 9, 1939.

be expected to develop dystocia in labor or who did have unpredicted dystocia were in the selected group. Two hundred and forty-seven were studied ante partum and 153 during labor or in the post-partum period. The 247 had been classified clinically, either as generally contracted, male type pelvis, generally contracted funnel, or as simple flat pelvis. The 153 patients who developed unanticipated dystocia in labor had been diagnosed clinically as having normal pelvis. During the period in which this study was conducted, the operative incidence in clinic cases at the hospital was 10.12 per cent, and the cesarean section incidence was 1.6 per cent.

The types and the frequency with which they occur in this study are shown in Table I.

The incidence of mixed types is shown in Table II.

TABLE I. PURE AND MIXED TYPES WITH PERCENTAGES: 400 CASES

	TOTAL	PER CENT	PURE	PER CENT	MIXED	PER CENT
Gynecoid	224	56.00	113	28.25	111	27.75
Android	95	23.75	50	12.50	45	11.25
Anthropoid	69	17.25	56	14.00	13	3.25
Platypelloid	12	3.00	11	2.75	1	0.25
Total	400	100.00	230	57.50	170	42.50

TABLE II. INCIDENCE OF MIXED TYPES

	NUMBER	PER CENT
Gynecoid	113	28.25
Gynecoid: narrow forepelvis	59	14.75
Gynecoid: anthropoid	36	9.00
Gynecoid: platypelloid	15	3.75
Gynecoid Misc.	1	0.25
Android	50	12.50
Android: gynecoid	18	4.50
Android: anthropoid	18	4.50
Android: platypelloid	9	2.25
Anthropoid	56	14.00
Anthropoid: gynecoid	13	3.25
Platypelloid	11	2.75
Platypelloid Asym.	1	0.25

Gynecoid Type.—Two hundred and twenty-four cases were found at the completion of the study to have a gynecoid type pelvis. One hundred and thirteen were the pure type and 111 were of the mixed type. The majority of the patients were small or average in size, but 60 were of more than average size. There were 138 who had been studied ante partum and 86 who are included because they developed dystocia in labor. Twenty-four patients, in the group studied ante partum, developed dystocia, while the other 114 were delivered normally.

The pure gynecoid type occurred twice as frequently as any other type. Delivery was spontaneous in 65 of these cases. Inlet dystocia, requiring cesarean section, developed in 9 patients in whom the pelvis was small or of average size, yet only one had an anteroposterior diameter below 10.5 cm. Oversize of the fetus was a factor in the disproportion in the majority. Arrest of the head at or below the level of the spines of the ischium took place in 39 patients. In this group the side wall convergence was greater and the interspinous diameter nearly 1 cm. less than in the group that delivered spontaneously. In 19 of the 32 patients requiring midforceps delivery, the occiput remained persistently posterior or in transverse arrest. Prolonged labor occurred in all of the cases in this latter group, the average in

the patients with transverse arrest being forty hours and in those with the occiput posterior over twenty-two hours. There was a 10 per cent increase in operative delivery in small- over large-sized pelves. The pure gynecoid type of pelvis, with its rounded inlet, wide subpubic arch, and average-sized sacrosciatic notch has been considered to be the normal female pelvis; yet it was found in this selected group that prolonged labor (over twenty-four hours) occurred in 30 cases, and that operative delivery was often difficult without evidence of bony disproportion being present.

The lower pelvis was considerably modified when the gynecoid type was associated with a narrow fore pelvis. The subpubic arch was narrower than in the pure form, side wall convergence was more marked, and, as a result, the lower pelvic diameters were considerably shorter. The pelvis in general was of small or average size. Inlet dystocia occurred in 6 of the patients, and arrest in labor at the level of the ischial spines was frequent, occurring in 24 cases. Very few in this group were recognized clinically as patients that might develop dystocia. Twenty-two were multiparas with a history of one or more difficult operative deliveries in previous labors; of these, 12 again had difficult labor requiring operative assistance. This proved to be a dangerous type of pelvis, possessing many of the characteristics of the android. Labor was frequently prolonged and vaginal delivery with forceps was often very difficult.

The gynecoid pelvis when associated with the anthropoid type of forepelvis was found to be of large or average size in three-fourths of the cases, yet prolonged labor was frequent. The narrow subpubic arch that is characteristic of the anthropoid pelvis was found in more than two-thirds of these cases, and it was associated with marked side wall convergence, producing much shorter diameters in the lower pelvis than are usually found with the gynecoid inlet. Arrest of the fetal head at the pelvic brim was uncommon but low pelvic arrest occurred in more than half the cases. The narrowing in the lower pelvic diameters and the sharper subpubic angle undoubtedly aid in part in producing dystocia in this type of pelvis.

Android Type.—This type of pelvis was found 95 times, being the second most frequent in the study. It was in pure form in 50 cases and in mixed form in 45 cases. Sixty-six women with android type pelvis were studied ante partum, because it was thought difficult labor was probable from the clinical findings, but 37 of these delivered spontaneously, although labor was frequently prolonged. Also included in this group are 29 patients who developed dystocia in labor. Stereoroentgenograms taken in the puerperium showed the android type pelvis.

In the pure android type, 12 were small, 15 average, and 23 large-sized pelves. The conjugata vera in pure android averaged 11 cm., but because the inlet had a wedge-shaped form, dystocia was frequent at that level. In very few instances was the head engaged at the onset of labor and the first stage was prolonged as the head descended transversely to the level of the ischial spines. Progress was difficult to judge and delay at the lower levels of the pelvis was just as frequent as at the inlet. The average duration of labor was longer than in any other type, being over twenty-two hours. Definite narrowing of the subpubic arch was found in all cases and convergent side walls in all but 7 of the cases. The average interspinous and intertuberosity diameters were 10.3 cm. and 10.6 cm. Disproportion was twice as frequent at the inlet as in the pure gynecoid pelvis. Twelve cesarean sections were necessary for arrest at the inlet, because the head was unable to adjust itself in a manner to permit descent. Dystocia in the lower pelvis occurred 18 times.

Available space low in the pelvis was limited by the convergence of the side walls and the forward curve of the sacrum which shortens the posterior segment. For this reason forceps delivery was often a difficult procedure. Clinical pelvimetry in android type pelves is misleading and inadequate. Stereoroentgenograms are especially valuable as the shape of the inlet and the configuration of the mid-pelvis can be detected only by this means.

Dystocia in the mixed forms of android was frequent, being especially common in the android with anthropoid tendency where outlet narrowing was marked.

Anthropoid Type.—This type was found 69 times, 56 in pure form and 13 in mixed form. Of the 36 patients studied ante partum 6 developed dystocia. Thirty-three other cases are included that developed dystocia in labor. The anthropoid type is generally adequate in all its internal diameters, even though there is relative transverse narrowing of the pelvic brim. In typical form the average transverse was 12 cm. and in the anthropoid with gynecoid tendency it was 12.4 cm. In 5 cases only was the transverse 11 cm. or less. Marked side wall convergence and a sharp subpubic angle were present in all but 10 cases, and the outlet diameters were the smallest found in any type. The average interspinous diameter was 9.6 cm. and the intertuberous 9.9 cm. Inlet dystocia was uncommon but arrest of the head low in the pelvis occurred 25 times. The head most frequently descended through the pelvis obliquely posterior and became arrested at the level of the ischial spines.

Many of the cases that had a spontaneous delivery had no difficulty in rotating from a posterior position, because the backward curvature of the sacrum was more marked, giving a wider posterior segment low in the pelvis.

In the mixed form, operative interference was necessary 10 times for the same indications as in the typical form.

Platypelloid Type.—This type was found 11 times in typical form, once as an asymmetrical flat pelvis, 15 times as gynecoid with platypelloid tendency, and 9 times as android with platypelloid tendency. The pelvic inlet offered the chief difficulty to descent. The subpubic arch was well rounded and the side walls parallel. The diameters in the lower pelvis were wider than average. In the parent type, dystocia at the inlet occurred 4 times for which cesarean section was done. In three of these, the conjugata vera was 8.8 cm. or less. Midpelvic arrest occurred 4 times.

Mixed types occurred 25 times and 14 of this group had normal, uncomplicated delivery. In 7 dystocia at the inlet occurred, and in 4 cases, arrest of the head at a low level in the pelvis made delivery by midforceps necessary.

TABLE III. DELIVERY IN PELVIC TYPES

	TOTAL	SPONTANEOUS VERTEX	SPONTANEOUS BREECH	LOW FORCEPS	MIDFORCEPS	CESAREAN SECTION	VERSION AND EXTRACTION	BREECH EXTRACTION	VAGINAL HYSTEROTOMY	NUMBER OPERATED
Gynecoid	113	63	3*	6	32	9		1		48
Gynecoid: narrow forepelvis	59	27	2	6	16	6		1	1	30
Gynecoid: anthropoid	36	11	1	1	18	3		2		24
Gynecoid: platypel- loid	15	8	1*	0	2	5		0		7
Gynecoid Misc.	1	0	0	0	0	1		0		1
Android	50	19	1	0	14	12	3*	2		31*
Android: gynecoid	18	7	0	1	5	4		1		11
Android: anthropoid	18	4	0	0	8	4		1	1	14
Android: platypelloid	9	6	0	0	2	1		0		3
Anthropoid	56	25	2	2	23	4		0		29
Anthropoid: gynecoid	13	3	0	0	9	1		0		10
Platypelloid	11	3	0	0	4	4		0		8
Platypelloid Asym.	1	0	0	0	0	1		0		1

*Twins.

Table IV is a summary showing the type of pelvis and where arrest occurred and indication for delivery.

Conjugata Vera.—Estimation of the length of the conjugata vera from the diagonal conjugate has been an important part of clinical pelvimetry, although it is recognized that the method is frequently unreliable. Clinical classification of contraction has depended on finding a conjugata vera of 10 cm. or less. While

TABLE IV

	GYNECOID	GYNECOID NARROW FORE P.	GYNECOID ANTHROPOID	GYNECOID PLATYPELLOID	GYNECOID MISC.	ANDROID	ANDROID GYNECOID	ANDROID ANTHROPOID	ANDROID PLATYPELLOID	ANTHROPOID	ANTHROPOID GYNECOID	PLATYPELLOID	PLATYPELLOID ASYMMETRICAL	TOTAL
Inlet arrest														
Cesarean section	9	6	3	5	1	12	4	4	1	4	1	4	1	55
Midpelvic arrest	10	10	10	1		9	1	4		17	6	2		70
Persistent posterior														
Transverse arrest	9	5	1	1		2	1		2		1	1		23
Breech extraction	1	1	2			2	1	1						8
Version and extraction						3*								3*
Cervical dystocia		1						1						2
Outlet dystocia	19	7	8			3	4	4		8	2	1		56
Total operations	48	30	24	7	1	31	11	14	3	29	10	8	1	217
Fetal deaths	3	2	3	0	0	7	3	2	0	0	0	0	0	20

*Twin.

a short conjugata vera usually indicates that the pelvis is small, it does not always mean that dangerous dystocia will follow. The size of the fetus is important in these cases. It would seem, however, that the variations in the shape of the inlet, even when no actual cephalopelvic disproportion exists, may prove of the greatest importance. There were 43 patients who had a conjugata vera of 10 cm. or less. It was found 10 times in the gynecoid type, 18 in android, and 12 times in the platypelloid type; 17 patients in whom it was between 9 and 10 cm. delivered normally, and 9 in the same group were delivered with low or midforceps, while 11 patients required cesarean section. In 6 patients with a conjugata vera between 8 and 9 cm., 4 required cesarean section, 1 delivered normally, and 1 was delivered with midforceps. In each type pelvis, cesarean section was performed 5 times.

Fetal Deaths.—Eight stillbirths and 12 neonatal deaths in which bony dystocia was a factor occurred in the 400 cases. Eight deaths were associated with the gynecoid type pelvis and 12 with the android type. In 15 cases in which fetal death occurred the labor was prolonged over twenty-four hours. Cerebral hemorrhage occurred in 9 cases. Asphyxia was the cause of death in 5 cases where version and extraction or breech extraction was the method of delivery. Intrauterine asphyxia associated with hard labor caused death in 6 cases. The type of pelvis played an important part in the deaths in 17 of the cases. These pelvises had a narrow subpubic angle and some degree of outlet contraction. Operative delivery was often difficult because of the funnel tendency. We have noted elsewhere in the paper that the narrow subpubic arch is frequently associated with difficult labor, and it has also been noted by Pettit⁶ as a factor in producing dystocia.

COMMENT

Stereo-roentgenographic study of the pelvis has revealed the variety of shapes that the female pelvis may assume and makes a more accurate classification possible, particularly through the recognition of the many mixed forms. Although our cases were selected in a different

way than were those of Heaton,⁴ Steele and others,⁵ Pettit and others,⁶ or Rappaport and Scadron,⁷ the percentages of the various types approximate their findings and those of Caldwell, Moloy and D'Esopo,³ and agree with a consecutive series of cases at the Providence Lying-In Hospital taken subsequent to this study.

A prognosis of dystocia based upon clinical pelvimetry alone proved to be inadequate. In this study only 25.5 per cent of the pelvises considered to be contracted clinically, actually developed dystocia. Conversely, it is our experience that abnormal pelvises were frequently difficult to diagnose clinically and often give rise to unexpected dystocia. While roentgenography may give warning that difficulty can arise in labor, it proved reliable for prognosis in only a small number of cases. Spontaneous deliveries have occurred often where difficulty was expected both from pelvic configuration and measurements. Elective cesarean section was performed but once on the basis of the x-ray findings alone. This was in a case with extreme outlet contraction. We have preferred to give an adequate test of labor in all other cases where disproportion was suspected. There is great danger that too much reliance will be placed on the roentgenologic examination by the inexperienced obstetrician. To use this method most successfully cooperation of the roentgenologist and obstetrician is essential for the proper evaluation of dystocia. It should prove to be of most value when the obstetrician acquires a knowledge of stereoroentgenography and uses it to supplement his clinical experience.

The influence which the form of the pelvis has in producing dystocia can be shown with stereoroentgenograms. The variations in the shape of the inlet that can be demonstrated and the importance that convergence of the side walls has in producing lower pelvic contraction is clearly revealed. In the android pelvis, the wedge-shaped inlet, even though its dimensions may be large, explains many cases of arrest at the pelvic brim. The head is unable to enter the inlet because the widest transverse diameter is so far posterior, and the forepelvis is so angulated that it is obstetrically useless. Increased side wall convergence and the forward curvature of the sacrum shorten the lower pelvic diameters and are frequent factors in producing dystocia at the pelvic outlet. In the anthropoid pelvis, transverse narrowing often delays the proper adjustment of the fetal head to the long anteroposterior diameter of the inlet, and the shorter outlet diameters frequently arrest the head in the posterior position at the level of the spines of the ischium.

In the platypelloid pelvis, dystocia at the inlet in our patients was caused by cephalopelvic disproportion due to a short conjugata vera.

The narrow forepelvis and a sharp subpubic angle are important in producing dystocia in the mixed gynecoid forms as well as in those of the android and anthropoid type. One hundred and thirty-nine patients in this series who had dystocia were found to have a smaller retropubic angle, and a sharp subpubic angle associated with increased convergence of the side walls. In the group of 100 multiparas studied because of previous difficult labor, 36 again required operative assistance and 28 of these had a type of pelvis with a sharp subpubic angle and a narrow forepelvis.

It is more difficult to understand what the causes of dystocia are in some of the pelves of the pure gynecoid type. Oversize of the fetus in the small and average-sized pelves accounts for the majority of cases of inlet dystocia in this study. We have noted a slight decrease in the lower pelvic diameters in cases of outlet dystocia, but equally large babies were delivered normally through similar or smaller diameters.

There are many pelves in which bony obstruction does not account for all the difficulties encountered. Unyielding soft parts, ineffectual expulsive forces, and the ability of the fetal head to mold easily, all have an important bearing on the successful culmination of labor and have to be considered in estimating the factors that produce dystocia.

Stereo-roentgenography has been a great aid in the management of patients requiring operative intervention. It emphasizes the danger of using a routine method of procedure when forceps delivery is necessary in pelves which are not uniform in shape. We have attempted to use the most advantageous pelvic diameters for traction and the proper levels at which to attempt rotation. As a result, the frequency of difficult forceps delivery has been greatly reduced.

CONCLUSIONS

1. Classification into type has been found to be accurate and adequate for clinical use.
2. Stereo-roentgenography helps explain many of the causes of dystocia.
3. The information gained by the use of this method has been valuable in selecting the best type of operative procedure.
4. Although it is a valuable adjunct to our armamentarium, it cannot supersede clinical experience.

We wish to express our gratitude to Dr. Bertram H. Buxton, Chief of Staff of the Providence Lying-in Hospital, under whose supervision this study was conducted, and to Dr. Russell R. Hunt, the Roentgenologist at the Hospital, for his cooperation.

REFERENCES

- (1) *Caldwell, W. E., and Moloy, H. C.*: AM. J. OBST. & GYNEC. **26**: 479, 1933.
- (2) *Moloy, H. C.*: AM. J. ROENTGENOL. **30**: 111, 1933. (3) *Caldwell, W. E., Moloy, H. C., and D'Esopo, D. A.*: AM. J. OBST. & GYNEC. **28**: 482, 1934. (4) *Heaton, C. E.*: New York J. Med. **38**: 83, 1938. (5) *Steele, K. B., Wing, L. A., and Mc-Lane, C. M.*: AM. J. OBST. & GYNEC. **35**: 938, 1938. (6) *Pettit, A. V., Garland, L. H., Dunn, R. D., and Shumaker, P.*: West. J. Surg. **44**: 1, 1936. (7) *Rappaport, E. M., and Scadron, S. J.*: J. A. M. A. **112**: 2492, 1939.

221 THAYER STREET

DISCUSSION

DR. ROBERT L. DENORMANDIE, BOSTON, MASS.—Does x-ray pelvimetry tell us more than intelligent clinical study does? Unquestionably in some cases it will. Is diagnosis of probable dystocia so certain by x-ray that we can rely on it implicitly? Dr. Walsh answers this very clearly and honestly. Even in the pure gynecoid type, the normal female pelvis, he found labor often prolonged and operative delivery often difficult. In only one case did Dr. Walsh do an elective section because of x-ray finding and that because of extreme outlet contraction. I am sure he would have done the same without the help of the x-ray.

Dr. Walsh states that clinical pelvimetry in the android type pelvis is misleading and inadequate, and that the shape of the inlet and configuration of the mid-pelvis can be detected only by stereo-roentgenograms. That seems to me a bit too

sweeping a statement, for I am sure I have recognized by vaginal palpation diameters inadequate to pass the fetus successfully.

Dr. Walsh clearly states the limitations of x-ray pelvimetry when he says the size of the fetus is important and that the x-ray fails to help us at all on the type of labor we may expect or the moldability of the fetal head.

DR. J. BAY JACOBS, WASHINGTON, D. C.—The technique of pelvic roentgenography has never received widespread use in clinical obstetrics. To me, this is an indication that many obstetricians do not consider it a reliable procedure. Also, they may have come to doubt its value, because too much dependence has been placed upon the inexperienced opinion of the roentgenologist. The obstetrician should himself be familiar with an accepted, simple technique, which he must direct the roentgenologist to follow. The interpretation of all films and the prediction of prognoses should be the duty of the obstetrician.

Dr. Walsh has made it clear that relatively small proportion of the patients in whom difficulty might be expected, actually develop dystocia. This should not underrate the importance of such study in your opinion, because it merely means that the range of observation is such as to detect almost all potential abnormalities rather than overlook any.

For the benefit of men who have not employed x-ray for pelvic mensuration or prognostication, I should like to differentiate between some of the commonly used terms and procedures.

Until recently roentgen pelvimetry was concerned principally with the pelvic inlet, which in my opinion is still and shall always be the most common seat of dystocia. With the use of a single film, we have been able to observe the contour of the inlet, and determine its measurements, as well as anticipate the mechanism of engagement. The value of this procedure is evident.

After Caldwell and Moloy called attention to pelvic architecture, especially as viewed from the lateral aspect, I instituted a technique of lateral pelvimetric roentgenography. This procedure is simple, rapid, accurate, and requires only one film. So much information may be obtained, that in my opinion, every borderline case warrants such study.

In 1929 Johnson described his technique of stereoroentgenometry. By this means, two views are made of the same object, just as it would be seen by each of your two eyes separately. Utilizing the two films and his apparatus known as the stereoroentgenometer, the points designating pelvic diameters may be located in space, and the distances between them may be readily measured. This impresses me as being the most accurate method of pelvimetry, although the technique is too complicated for general use.

By stereoroentgenography is meant the placing of two stereoscopic films in the stereoscope, and the actual visualization of the pelvis in three dimensions. Should the precision stereoscope be used, one may be able to measure pelvic diameters in space. This is a refined procedure, but it necessitates expensive apparatus, and as employed by the author, requires four films for one complete pelvic study. Besides the disadvantage of expense, which is frequently a factor, many other items must be considered.

After studying several hundred lateral pelvigrams, I have come to the conclusion that the true conjugate diameter is still the most important pelvic dimension, and that it bears no definite relationship to the diagonal conjugate. I take my pictures in the standing posture, and have observed that in the vast majority of instances the head tries to engage with the biparietal diameter in the true conjugate.

DR. GEORGE F. PENDLETON, KANSAS CITY, Mo.—I am particularly impressed with what you and I call the simple contracted pelvis in the gynecoid type. We in Kansas City are in a city, almost wholly American, but we do see a lot of simple contracted pelvises which would still go in the gynecoid group. If a measurement is made early and again in the latter part of labor, you will sometimes be surprised how it has increased in size. It is an important practical point that we make use of quite often.

DR. FREDERICK H. FALLS, CHICAGO, ILL.—There is no question that pelvic measurements change from early pregnancy to the end of pregnancy, and particularly during labor. We forget that the pelvis is made up of numerous joints and that during pregnancy those joints are softened.

DR. WILLIAM T. McCONNELL, LOUISVILLE, KY.—It is chiefly of academic value to know the pelvic measurements when labor sets in. What we want to know is whether or not that particular head can easily go through that particular pelvis at that particular time. Now there is a whole lot we can tell without x-ray. I do not know how one can tell all there is to be known, however, unless he is himself familiar with some x-ray technique.

DR. LEROY A. CALKINS, KANSAS CITY, MO.—I would like to ask Dr. Walsh if he has taken any x-ray pictures of the inlet contractions with the woman in the Walcher position? Has he also taken any pictures of the outlet contraction with the woman in the exaggerated flexion of the thighs on the abdomen position?

In our clinic more than 90 per cent of all cases of dystocia are due to poor labor pains, again bringing in the point that perhaps it is an endocrine dystocia and not a pelvic dystocia. Dr. Walsh's figures would indicate, by implication at least, that such might be the case.

DR. WALSH (closing).—This method of study of the pelvis is admittedly expensive. We were trying to get acquainted with this form of x-ray pelvimetry, and we began by studying cases ante partum to acquire some knowledge of the configuration of the pelvis. We have made only a few measurements in labor.

I do think that a knowledge of stereoroentgenography needs to be acquired by the clinician or the obstetrician, and he can acquire this only by collaboration with the x-ray man.

We feel that as we have gone on, since March, 1939, using this method less frequently, that we use it more successfully because we have now a greater knowledge of the pelvis.

Replying to Dr. Calkins, we have not attempted to see whether there was an increased diameter after change of posture. We do not have the x-ray machine on the delivery floor.

STRUMA OVARIUM*

H. M. N. WYNNE, M.D., J. S. MCCARTNEY, M.D., AND
J. F. MCCLENDON, M.D., MINNEAPOLIS, MINN.

THYROID tissue is frequently found in dermoid cysts and teratomas, either as one of the elements composing these complex tumors or as the predominating tissue. Occasionally an ovarian tumor is composed entirely or almost entirely of thyroid tissue and then is called struma ovarii.

The frequency with which thyroid tissue has been found in ovarian teratomas by various authors is shown in Table I. The marked differences in this incidence as reported by these authors may perhaps be related to the efforts made to demonstrate its presence. In a single section, none of this type of tissue might have been present, whereas multiple sections might have revealed it.

*Read at the Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 7 to 9, 1939.

TABLE I. INCIDENCE OF THYROID TISSUE IN TERATOMAS OF THE OVARY

	TERATOMAS AND DERMOIDS	WITH THYROID TISSUE	PER CENT
Meigs	27	2	7.4
Pick	21	6	28.5
Rohdenburg	61	9	14.7
Shaw	23	5	21.7
Spencer	66	1	1.5
	198	23	11.6

Gottschalk in 1899 is said first to have described the tumor under the diagnosis of folliculoma malignum ovarii. Later Kretschmar described a similar tumor which he at first called an endothelioma and later a thyroid metastasis. Pick in 1902 is credited with first recognizing the tumor as thyroid tissue.

Several explanations of the source of the thyroid tissue in the ovary have been advanced. Metastases from a normal or an adenomatous thyroid and metastases from carcinomas of the thyroid are opinions that have now been discarded by pathologists. It is certain that most of the tumors described are teratomas because of the presence of other types of tissue. The pure thyroid tumor of the ovary is believed to be a unilateral development of a teratoma.

The argument of Bauer that struma ovarii is not thyroid tissue but a colloid degeneration of pseudomucinous cystadenomas is refuted by several facts: (1) the morphology and stain-reaction of the tumors are similar to thyroid gland tissue; (2) the chemical examinations have showed the presence of iodine in some and the absence of pseudomucin in all tumors examined (Plaut); (3) the feeding of tadpoles with tumor tissue or with thyroid gland produces precocious growth and development (Plaut).

CLINICAL SIGNS AND SYMPTOMS

There are no clinical symptoms or signs that can be depended upon to differentiate a struma ovarii from an ordinary teratoma. It is said that ascites is a common finding. Only three cases (Kovaes', Kleine's, Moench's) have been reported which showed any suggestion of hyperthyroidism relieved by the removal of the ovarian tumor. Several patients had struma of the neck. One patient developed a mild hyperthyroidism following operation (Trapl's).

The great majority of the reported cases were clinically benign. A few of the patients remained well five or more years following operation, but most of the follow-up reports are incomplete and cover too short a time to be of much value.

Several cases were definitely malignant. Werth found metastases in the peritoneum of the bladder and anterior rectal wall. Shapiro found omental metastases. Boxer's patient died five years after operation of metastases in the liver. Proescher and Roddy's patient (Case III) died five months after operation and had metastases in the liver, mesentery, and omentum. Kretschmar's patient died less than two years after operation of probable recurrence.

CASE REPORT

Miss L. M. O., aged 26 years, white, was referred by Dr. Reuben Johnson, Jan. 16, 1937. For the past six to eight months she had had a heavy feeling in the lower right abdomen when she ran to catch a streetcar. Two weeks before she was examined she had noticed a hard lump in the right side of the lower abdomen. She thought she had a "rupture." There had been no other symptoms.

Menstruation began at age 13 and had been regular about every thirty days. The flow had been normal in amount, lasting three to four days and painless.

She had never had any intermenstrual bleeding. The last period began Dec. 29, 1936. There had been no change in her periods for several years.

Physical Examination.—She was a healthy-looking young woman. There were no abnormalities except a firm, nodular, insensitive, movable mass in the pelvis about the size of a small grapefruit. The cervix and corpus were normal in size but displaced to the left of the midline. No enlargement of the thyroid was made out. No clinical signs of hyperthyroidism or of hypothyroidism could be elicited.

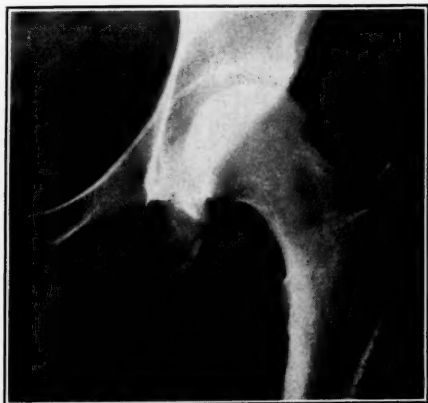


Fig. 1.—X-ray of left ischium, showing metastasis.



Fig. 2.—Photograph of gross specimen, showing external and cut surfaces.

Operation was performed Jan. 22, 1937. A solid, irregularly nodular tumor of the right ovary was removed. There were no adhesions. There was no ascites. Exploration of the abdominal organs revealed no other abnormality. The left ovary was of normal size and appearance. The patient recovered rapidly from the operation and returned to work March 1, 1937.

Pelvic examinations made at intervals since the operation have showed no evidence of recurrence in the pelvic organs.

The patient returned to Dr. Johnson Dec. 30, 1938, complaining of pain in the region of the right knee and right hip. There was tenderness on pressure over the

tuberosity of the ischium. X-rays of the pelvis showed a destructive bone lesion of the right ischial tuberosity and inferior ramus of the right pubis. X-rays of the chest showed no abnormality (Fig. 1).

Operation was performed Jan. 20, 1939, by Dr. E. T. Evans. Complete removal of the tuberosity of the right ischium and inferior ramus of the right pubis was done. The patient recovered quickly from the operation. A pelvic examination on July 24, 1939, showed no signs or symptoms of recurrence.

The specimen of the ovarian tumor was an olive-shaped mass measuring 9 by 6 by 6 cm. The external surface was for the most part smooth, although there were a few rounded nodular elevations. Gross section showed a variegated appearance. The major portion was composed of spaces filled with firm transparent brown colloid. One



Fig. 3.

Fig. 3.—Photomicrograph of primary tumor of area, showing well-differentiated thyroid tissue with large amounts of colloid. $\times 300$.

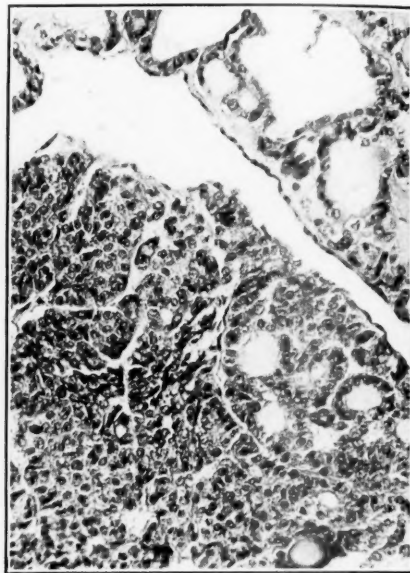


Fig. 4.

Fig. 4.—Photomicrograph of primary tumor of area, showing adenocarcinoma. $\times 300$.

multilocular cyst, filled with clear fluid and measuring 4 by 3 cm., was present. A solid area of pale, yellowish white tissue, apparently made up of coalescing smaller masses, comprised the balance of the tumor mass. No hair, sebaceous material, or mucus was seen (Fig. 2). Slicing into blocks of 5 mm. thickness revealed no appearance other than that noted on the first section.

Microscopic examination of two apparently representative areas showed what appeared to be approximately normal adult type of thyroid tissue, with acini full of colloid. In a few areas there seemed to be some piling up of the cells, but no acinar structures of the type found in exophthalmic goiter were present. In one place there was a suggestion of invasion of a blood vessel. Occasional mitotic figures were found. In no portion was there any type of tissue except thyroid (Fig. 3). The diagnosis was a benign teratoma with a unilateral line of development, only thyroid tissue being present. After the metastatic tumor was found in the ischium, six more blocks were taken from the original tumor for microscopic examination. This examination showed a much more undifferentiated type of thyroid tissue than was present in the first two blocks. In these sections the structure was that of fairly typical adenocarcinoma (Fig. 4). Some solid areas con-

taining no colloid were found. In none of the eight sections was anything found resembling tissue other than thyroid. A small amount of ovarian stroma and a few follicular cysts were present in one block.

Specimen of Ischium: The bone was replaced in an area 6 by 4.5 by 4 cm. by soft shiny gelatinous tissue. It was not slimy. No solid areas were noted. Microscopic examination (Fig. 5) showed a structure readily recognizable as being that of thyroid tissue. It was not quite so well differentiated as that found in the first two blocks from the ovarian tumor but better differentiated than that in some areas of the other six blocks. The ischial tumor might easily have passed for an actively growing benign adenoma of the thyroid gland. No tissue other than thyroid was present in the ischial tumor.

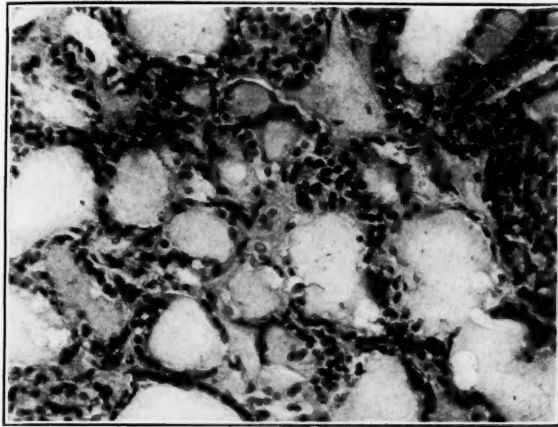


Fig. 5.—Photomicrograph of metastasis in ischium, showing well-differentiated thyroid tissue. $\times 300$.

Since it appears from the literature that microscopic examination alone does not suffice for the recognition of thyroid tissue, one of us analyzed the ovarian and ischial tumors by the method of McClendon-Bratton. The results of the tests are shown in Table II.

The apparent discrepancies in the analyses of the ovarian and ischial tumors are doubtless to be explained by the fact that the examination of the ovarian tumor was not made until after more than two years' immersion in 10 per cent formalin.

TABLE II
(Micrograms per Kilogram)

	TOTAL IODINE		THYROID HORMONE IODINE	
	WET MICROGRAMS	DRY MICROGRAMS	WET	IN DRY PROTEIN FRACTION
Colloid from struma ovarii (2 years in formalin)	22,500		1,310	5,140
Ischial metastasis (2 months in formalin)	9,100		3,230	28,300
Ovary (Baumann and Metzger)	6 to 60			
Struma ovarii				
Robert Meyer		14,000		
Neu		20,000		
Plaut Spec. I		673,000		
II		25,000		
III		00,000		
Normal thyroid (McClendon)		120,000 to 5,940,000		

This long exposure to the action of formalin caused a large amount of iodine to be freed from the protein fraction, but it still appears as total iodine. For purposes of comparison it is to be noted that normal tissue other than thyroid contains about 40 to 80 micrograms of hormone iodine per kilogram (Baumann and Metzger found but from 6 to 60 micrograms of total iodine per kilogram of normal ovary). A certain comparison can hardly be drawn between the analyses of Meyer, Neu, and Plaut, and those made by us of the ovarian and ischial tumors and the values given for normal thyroid tissue. The thyroid hormone values of 5,140 to 28,300 are more like those of thyroid tissue than of nonthyroid tissue. There seems to be no doubt that the thyroid hormone was manufactured in the struma ovarii and ischial tumor and not merely derived from the thyroid gland, as it would be in much smaller concentration if the latter were true. The table shows that the primary tumor from our case contained from 375 to 3,750 times as much iodine as reported by Baumann and Metzger for the normal ovary.

SUMMARY AND CONCLUSIONS

An instance of malignant primary unilateral teratomas of the ovary composed entirely of thyroid tissue is reported. The ischial metastasis also contained only thyroid tissue.

At no time was there any evidence that this tumor tissue caused the symptoms of hyperthyroidism or that it substituted for the secretion of the normal thyroid gland.

REFERENCES

- (1) *Bauer, E.*: Ztschr. f. Geburtsh. u. Gynäk. **75**: 1914. (2) *Baumann and Metzger*: J. Biol. Chem. **127**: 111, 1939. (3) *Boxer*: Zentralbl. f. Gynäk. **35**: 51, 1911. (4) *Frankl, O.*: Ibid. **58**: 2706, 1934. (5) *Gottschalk, S.*: Arch. f. Gynäk. **59**: 676, 1899. (6) *Kleine, H. O.*: Ibid. **158**: 62, 1934. (7) *Kovacs, F.*: Ibid. **122**: 766, 1924. (8) *Kretschmar*: Monatsschr. f. Geburtsh. u. Gynäk. **19**: 389 and 546, 1904. (9) *McClendon, J. F.*: Iodine and the Incidence of Goiter, 1939, University of Minnesota Press. (10) *Meigs, J. V.*: Tumors of the Female Pelvic Organs, New York, 1934, the Macmillan Company. (11) *Meyer, R.*: Ergebn. d. Path. Anat. Lubarsch. Ostertag. Jahrg. **15**, Abt. I, 1911. Virch. Arch. **173**: 538, 1903. (12) *Moench, G. L.*: Ztschr. f. Geburtsh. u. Gynäk. **77**: 30, 1915; Surg. Gynec. Obst. **49**: 150, 1929. (13) *Pick*: Berl. Clin. Wehnschr. **19**: 443, 1882; Berl. med. Gellsch. **4**: 26, 1902. (14) *Plaut, A.*: AM. J. OBST. & GYNEC. **25**: 351, 1933. (15) *Proescher and Roddy*: Ibid. **61**: 619, 1910. (16) *Rohdenburg, G. L.*: J. Lab. & Clin. Med. **12**: 211, 1926. (17) *Shapiro, P. F.*: Ann. Surg. **92**: 1031, 1930. (18) *Shaw, W.*: J. Obst. & Gynaec. Brit. Emp. **39**: 825, 1932. (19) *Spencer, H.*: Proc. Roy. Soc. Med. **26**: 1438, 1933. (20) *Trapf, G.*: Ztschr. f. Geburtsh. u. Gynäk. **70**: 192, 1912. (21) *Werth, G.*: Zentralbl. f. Gynäk. **52**: 2944, 1928.

DISCUSSION

DR. JAMES E. DAVIS, ANN ARBOR, MICH.—It is true that thyroid tissue occurs in teratoblastomas in a frequency of 11 to 12 per cent. Yet this is not a figure of great frequency when one considers that in the group of body tumors teratoblastomas make up only a fair percentage. The frequency of the entire group of teratoblastomas has been given by Miller as 10.9 per cent in a whole group of 21,953 miscellaneous ovarian tumors.

Thyroid tissue in a teratoblastoma will in most instances show numerous areas in which the vesicles are quite immature. The vascular supply is uncertain, and opportunity for irritation of the vesicular epithelium is present. Therefore, one should expect a considerable percentage of these cases to develop ultimately into malignancies. It is very interesting that Dr. Wynne's case showed a metastasis to bone. This is not unusual in tumors of the thyroid gland.

The most attractive explanation of the formation of these tumors is that of the organizer theory which was first defined by Spemann. The organizers are

regarded by Huxley and De Beer as diffusible, labile agents which act upon the area of proliferation in the impregnated ovum about the time of formation of the primitive streak. The general effect of the organizer is to induce neighboring tissues to follow the axial plan of organization.

It is quite interesting in cases of teratoblastoma to look carefully into the family history. Quite recently I had the experience of finding three sisters with teratoblastomas. The mother had similar tumors. The mother's sister and a grandmother gave histories of teratoblastomas, all occurring at approximately the same age. Koltonski and also Luxenberger have reported like experiences.

DR. WYNNE (closing).—The left ovary in this patient was grossly normal. Examinations since the operation have shown no recurrence in the pelvis. The patient was a young woman who hopes to have children.

TRACHELOPLASTY (STURMDORF TECHNIQUE) IN THE TREATMENT OF STERILITY*

OREN MOORE, M.D., CHARLOTTE, N. C.

ALTHOUGH increased knowledge of endocrinology and of the physiology of fertilization and conception has increased our success in treating the nonfertile marriage, there is still a large percentage of sterile cases in which the cervix is the offender. In my own practice, it is believed that in approximately 60 per cent of all patients who present themselves for study, sterility may be finally charged against the cervix. This, of course, does not apply to that group which, due to massive pathology and indicated surgery, are obviously, at first glance, hopelessly and permanently out of the picture.

It is not believed, however, that in the surgical cases marked structural changes, stenoses, strictures, and the like are the predominating factors, but rather, that chronic endocervicitis of a glandular origin is to blame. These glands of the endocervix, being charged with the duty of producing mucus for lubricating and protective purposes, and being vulnerable in their location to bacterial attack, respond to the rather frequent incidence of infection by an excess production of tough and tenacious secretion.

This plug of mucus constantly present in the canal offers an effectual barrier to the escape of the sperm from the unfriendly acid atmosphere of the vagina into the more hospitable interior of the upper cervix and uterus for, while the male cell is aggressive in penetration, it is still feeble in power.

Kurzroek has stated that the lytic action of the semen on normal cervical mucus is not duplicated with regard to mucopurulent secretion, and Möench believes that the penetrability of the cervical mucus, by the sperm, varies directly with the viscosity of the plug. I agree entirely with this opinion and believe that I have observed, time after time, that the more acute infections, often with copious fluid discharges which

*Read at the Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., September 7 to 9, 1939.

flow out and leave the cervical canal unplugged, frequently allow pregnancy, whereas the low grade type of infection effectually prevents it.

No discussion is here attempted of the variability in chemistry of the mucus plug at different stages of the menstrual cycle for, as yet, proof of absolute and constant variations are not, to my knowledge, available. But, should this factor of chemical variability, with a consequent variability of penetration by the sperm, certainly exist, it still presents no argument against surgical attempts to remove the infected glandular structures. Surely it can be agreed that "mass action," "central stream progress," and kindred observations and beliefs in the rate of progress and method employed by the sperm in traversing the cervical canal, might readily be perverted if the secretion in the canal deviates markedly from the normal.

After an adequate and complete study of the individual case has ruled out all other factors, and when such a chronic and low grade endocervicitis, with its resultant plug, has been repeatedly demonstrated at different phases of the menstrual cycle and therefore believed to be constantly present, I have not hesitated to suggest a coring operation for the removal of the diseased glands.

After employing a number of methods I have reached the conclusion that, in my hands at least, the technique described by Sturmdorf offers more chances for success than any other. Its peculiar virtues, which include the preservation of circular fibers, the covering of the raw surface with healthy mucosa, and the lessened likelihood of disturbing hemorrhage, all recommend it.

The cost in time and money to the patient incident to a surgical procedure of this type is, of course, a factor which may be argued against it, and for this reason I, along with others, have attempted to achieve the same ends by electrical conization. Unhappily, the results have not been satisfactory, and indeed, in a few instances, complications such as hemorrhage, postoperative stricture, infection, and prolonged offensive drainage with delayed granulation have convinced me that Sturmdorf's technique is infinitely preferable.

(I pause here to observe that, since abandoning the coagulation feature after electrical conization, the frequency and severity of hemorrhage has been decidedly lessened.)

I have tried this modified Sturmdorf procedure on 79 selected cases; that is, selected because of the belief that the cervix alone was at fault, with the results that in 63 cases pregnancy followed within nine months; in 7 instances, before the next period was due, in 12, within two months, and the remainder scattered over the above-mentioned period. It may be properly argued that other factors conducive to pregnancy might have been spontaneously injected during a period as long as nine months. I cannot successfully dispute such a conclusion except to offer the evidence that the period of infertility in these 79 cases had varied from four to fourteen years, and that many other procedures had been attempted without results.

Further, I believe that in many cases of barren marriages, untreated, and with spontaneous recovery at and around the menopausal age, the

disappearance of the plug of mucus due to the atrophy of glandular tissues (which is a common occurrence at mid-life) results in a physiologic removal of the plug and a consequent opening of the canal.

In conclusion, I hasten to state that so many factors must be considered in a proper study of sterility that one single procedure such as discussed above should not be relied upon too completely; but when one recalls the zeal with which nature maintains the patency of any preformed canal, it would seem logical to render her aid and assistance in maintaining this function, and certainly the removal of infected glands of the internal cervix can be so regarded.

DISCUSSION

DR. QUITMAN U. NEWELL, ST. LOUIS, MO.—I have always regarded the causes of sterility in this order: first, an endocrine condition where the production of ova was poor. Second, I consider inflammatory changes in the cervix with a ropey discharge as a sterility factor.

I was very much pleased when Dr. Moore said he preferred the Sturmdorf operation for the correction of this condition. I am sure the conization method by the electric knife has its place in the treatment of chronic endocervicitis, but for some years I have resorted to the conical excision method (Sturmdorf) with the cold knife, feeling that the bleeding can be better controlled.

DR. IVAN PROCTOR, RALEIGH, N. C.—Dr. Moore has presented a procedure, which to us has offered very gratifying results, in relieving chronic pelvic disease, and also in increasing the chances of conception.

We divide cervicitis into four groups according to the extent of the disease: (1) Simple erosion; (2) extensive erosion and infection; (3) laceration, erosion, and infection; (4) multiple laceration, hypertrophy, and infection. The first is treated by simple radial cauterization with a thin, flat tip nasal cautery. The second by deep crucial incisions, then more superficial cuts with the cautery. The third by Sturmdorf tracheloplasty. The fourth in sterilized or postmenopausal patients by high amputation. Without preparation I am unable to give statistics on conception following treatment in the first three groups.

DR. HOWARD F. KANE, WASHINGTON, D. C.—In treating cervicitis in sterile patients I have in most cases used linear cauterization. I did that before making any further investigation, before doing the Hühner test, the Rubin test, or investigating the endocrine status of the patient.

Another point in sterility is interesting. I believe that 90 per cent of the women who come to me are the wives of men who are working mentally, young business or professional men, who are worried about their incomes, or their work, and I have been impressed with the large number of cases in which by studying the husband, we have found a somewhat lowered vitality of the sperms. This is almost always found in the mental worker.

It has also been my personal experience to take care of the wives of a number of baseball players. These men are, of course, very active physically, but the strain under which they are working when playing seems to have the same effect as on the men who are worrying about overdue bills, sick patients, etc. I have not seen a wife of a baseball player become pregnant during the baseball season, but they do become pregnant during the winter.

DR. ROLAND S. CRON, MILWAUKEE, WIS.—I would like to learn Dr. Moore's technique used to determine whether or not the sperms have penetrated the tenacious mucus of the cervix; whether he has been able to recover them from the fundal cavity, or whether in the introduction of the instrument to obtain the sperms, the sperms are carried up from below.

DR. L. A. GRAY, LOUISVILLE, KY.—The stem pessary seems to have fallen into considerable disfavor in recent years. However, at the Johns Hopkins Hospital it has been used steadily for many years and is still being used. We have never seen any infections from it, at least in one or two hundred cases. It is of particular value in antelexion, with the small cervix, allowing not only a large canal but producing hypertrophy of the cervix and uterus.

DR. D. N. BARROWS, NEW YORK, N. Y.—We used to do about 200 Sturmdorf operations a year at Bellevue under Dr. Holden. After perfecting our technique with conization and cauterization, we cut down the Sturmdorf operations to about ten a year.

DR. MOORE (closing).—I have delivered 47 women who have become pregnant after a cervical operation. We have found no difficulty at all with dilatation of the cervix and used no interference. Let me again stress that I was advocating this operation for a mild cervicitis and in nulliparous women. In my experience the Sturmdorf operation is the best of all operations devised for this condition, but it is for the woman who has not had a baby and who has what might be called a clean cervix.

As to Dr. Cron's question about how we discover whether the sperm cells have penetrated the cervical mucus I can say this: When finding them I have never been sure whether I had carried them up with my instrument or not. Our practice is to take a plug of mucus, and put it on a slide with some sperms from the husband. The action of the sperms appears perfectly normal under the microscope until they touch the plug of mucus when they become firmly enmeshed therein. In a short time they will die. If they do this on the stage of the microscope, they also undoubtedly do so inside of the cervix.

AN ELECTRIC TIMER AS AN AID IN COUNTING THE FETAL HEART IN THE SECOND STAGE OF LABOR AND IN TIMING AND SPACING FORCEPS TRACTION*

WALTER B. MOUNT, A.B., M.D., F.A.C.S., MONTCLAIR, N. J.

(From the Obstetrical Department, Mountainside Hospital)

THE importance of watching the fetal heart during labor has been stressed so often that its desirability may be granted. A variety of stethoscopes have been designed to facilitate counting the heart sounds, one of which, that of Falls,¹ carries a watch the dial of which is reflected in a magnifying mirror which one can see while listening. However, it was found that the watch cannot be read through the distance segment of bifocal lenses, that the special parts of the instrument are delicate and get out of order or broken, and that the ticking of the watch, intensified by bone conduction, may become annoying.

In 1926 von Wachenfeldt² devised a signal clock which rings a bell every fifteen seconds, a bell that one can hear while using a head stethoscope. It is made in Sweden and is run by a dry battery. In 1927 DeLee publicized his electric clock,³ which rings a bell every fifteen or every ten seconds. The original cost has been reduced, but one must be installed in each delivery room or labor room and all connected with a master clock. We present an electric timer (Fig. 1). It can be connected to any base plug with an alternating current. It is small and light (five inches square and weighing less than two pounds); it can be carried from one delivery room to another, or to another hospital, and can be used in home deliveries. It has not gotten out of order in the four years of its use. The bell can be heard

*Read, in modified form, at the Fifty-Second Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 7 to 9, 1939.

easily with a stethoscope in one's ears, yet the sound does not disturb the patient or others, so that often we all have forgotten to disconnect the instrument after a delivery.

By manipulating an arm at the back of our instrument one can at will have the bell sound every fifteen seconds, or every thirty seconds, or every minute. Freed⁴ states that the fetal heart should be counted for thirty seconds rather than for only fifteen seconds to insure accuracy. Moreover, in case forceps must be used, with this timer one then can watch carefully the duration of the forceps tractions and of the pauses between tractions. Smellie⁵ in 1756 directed to "pull gently during every pain; or if the pains are gone, at the interval of four or five minutes, that the parts may be slowly dilated, as they are in the natural labor." Unless one checks the time carefully when using forceps he is likely to hurry and to reverse nature's rule in the spacing of uterine contractions. For the purpose of accurately timing forceps tractions, the longer intervals in the timer are more convenient than the fifteen-second interval. Our hospital electric clocks do not lend themselves to these uses, because the hands move a whole minute at a time.

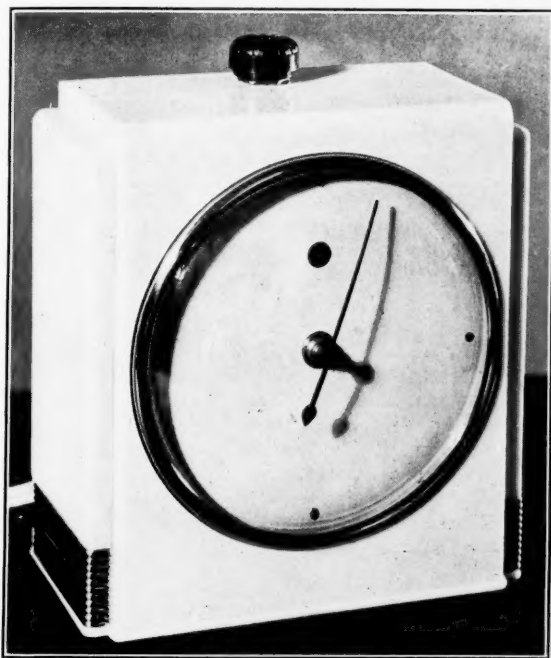


Fig. 1.—Electric timer.

The use of this instrument helps to emphasize and make easier of execution two important points in the management of the second stage of labor which often are slighted to the detriment of the fetus; namely, the frequent counting of the fetal heart and the timing and spacing of forceps tractions.

The fetal electrocardiogram and phonocardiographic records of the fetal heart are not practical late in labor. The various electrical devices for amplifying the fetal heart are expensive and so far not reliable at all times. In a recent survey only two of them were in working order. The DeCosta⁶ photostethoscope, the most recent, seems the best instrument of all, in that with each beat of the fetal heart an electric bulb flashes, so that rate and regularity are visible. Few of these devices are now obtainable.

This apparatus is manufactured by Malcolm Woodruff, Montclair, N. J.

REFERENCES

- (1) *Falls, F. H., and Hunter, T. A.*: AM. J. OBST. & GYNEC. 8: 356, 1924. (2) *von Wachenfeldt, S.*: Zentralbl. f. Gynäk. 50: 2372, 1926. (3) *DeLee, J. B.*: J. A. M. A. 88: 1000, 1927. (4) *Freed, F. C.*: AM. J. OBST. & GYNEC. 14: 659, 1927. (5) *Smellie, William*: A Treatise on the Theory and Practice of Midwifery, London, ed. 3, 1756 1: pp. 284-285. (6) *DeCosta, E. J.*: J. A. M. A. 111: 2008, 1938.

21 PLYMOUTH STREET

DISCUSSION

DR. SAMUEL A. COSGROVE, JERSEY CITY, N. J.—One must concur in what Dr. Mount says in his discussion of the necessity of watching the fetal heart during the second stage of labor, and in general of what he says as to the proper management of emergencies as indicated by significant variations in the heart rate. In the inexperienced, I have, however, noted undue alarm at transient or insignificant variations in the fetal pulse, and a tendency when they occur to attempt artificial interference under conditions which promise less favorable outcome for the fetus than dependence on the natural further evolution of the labor.

As Dr. Mount has properly pointed out, sometimes nothing can be done to improve the fetal chances. Indeed I would be inclined to think that this is true in most of the situations in which the behavior of the fetal heart causes concern for fetal survival. In many situations one had better resign oneself to the probable loss of the baby than resort inadvisedly to frenzied interference which may carry with it even greater hazard to the fetus, and perhaps definite danger to the mother.

Dr. Mount has been kind enough to permit me the use of two models of his timing device. Our delivery rooms are, however, each equipped with an electric clock, with a separate large second hand, jumping not at intervals of several seconds, but each second. We have found that the timing is more readily done by watching the second hand on these clocks than by the gentle musical note sounded by the device presented by Dr. Mount. This sound may frequently be lost in the variety of noises which may occur in the delivery room.

DR. FREDERICK H. FALLS, CHICAGO, ILL.—I am not in entire agreement with Dr. Mount's statement that rapid heart tones should not cause much concern. Heart tones above the normal maximum of 160 should be the object of close and repeated observation. Richardson has shown an interesting curve in the fetal heart rate in cases of incomplete separation of the placenta. The rate gradually increases up to 180 to 200 in the early stages of separation and as the separation becomes more complete the tones gradually become slower and weaker immediately preceding the death of the baby. I have confirmed this personally and have repeatedly operated in the early stage of the separation, while the heart tones were still rapid, and have secured a living baby.

Some years ago I devised an instrument which I labeled the vaginal stethoscope. I found that hearing and counting the fetal heart tones by placing the ball of the stethoscope against the lower uterine segment through the anterior vaginal wall was practical. The heart tones thus heard about the fourth lunar month are quite clear and strong but one must wait until the fetus turns within the uterus in such a way as to bring the back into apposition with the lower uterine segment.

DR. MOUNT (closing).—I should have mentioned Dr. Richardson's observation of the increasingly rapid fetal heart found in early ablatio placentae. It is still true that the rapid fetal heart is less often a sign of distress than the slow fetal heart.

In hospitals equipped throughout with electric timing clocks, no other device is, of course, necessary. Furthermore observation of the fetal heart during labor by another physician or a nurse will usually satisfy all requirements.

CHEMOTHERAPY IN OBSTETRICS AND GYNECOLOGY*

R. GORDON DOUGLAS, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, The New York Hospital and Cornell University Medical College)

THE recent introduction of sulfanilamide and related compounds into our therapeutic armamentarium, has revolutionized the present-day treatment in certain diseases of an infectious nature. In a relatively short time many investigators employing animal experimentation, pharmacologic studies, and clinical use by trial and error, have explored some of the actions and uses of the various compounds, in every known form of infection, and in some diseases of a noninfectious nature. Fortunately, the infections influenced the most by the drugs in question have proved to be of relatively common incidence and are diseases for which, with few exceptions, there is no other specific form of therapy available. The practitioner of obstetrics and gynecology is especially fortunate in that several most trying conditions are amenable to this new form of therapy.

An historical review is omitted at this time because of the many frequent reduplications in the current literature. The recent monograph by Long and Bliss¹⁵ contains a chapter with a very complete summary of the historical phases of the development of the various compounds and their uses.

Before proceeding to a detailed analysis of the data in question, I should like to mention two conditions essential, I believe, for successful treatment of patients in this field. The first is that the treatment should be under the complete supervision of the obstetrician or gynecologist, who must assume the responsibility for such therapy. After all, there are many fundamental problems associated with, for instance, the presence of *B. coli* in the urine of the obstetric or gynecologic patient. The problem is not so simple that the consulting internist or "sulfanilamide specialist" can immediately proceed with a plan of therapy. Therefore much knowledge based on our background of experience must be brought into play in deciding on the necessity of therapy, in observing the clinical progress, and in the evaluation of results. It is accordingly of the utmost importance, that all of us, who have these problems to face, should be able to manage successfully our own therapy.

The second point is the all important problem of accurate bacteriologic diagnosis before the commencement of therapy and its control during the period of treatment. There may occasionally be indications in the critically ill patient, for the use of the drug before the nature of the infecting organism is ascertained. Under such circumstances, the bacteriologic investigation can certainly be started, at the latest coinci-

*Read at a meeting of the New York Obstetrical Society, October 10, 1939.

dental with the therapy. A blood culture at this time may be of particular value, whereas if taken some hours later it may not reveal the true circumstances at the time of the onset of treatment. We would then have definite information concerning the infecting organism before our therapy has advanced very far. At no time in the past has prophylactic, prompt and accurate bacteriologic investigation of infections in obstetrics and gynecology been so well repaid, as far as the welfare of the patient is concerned, as it is today. Certain exceptions to the above principles must be made for patients in rural areas where laboratory facilities are not available. This excuse, however, cannot be accepted where the real reason is indifference or a lack of administrative or technical cooperation. A guiding principle where adequate laboratory facilities are available should be the early bacteriologic investigation of secretions, discharges or other material where the later possibility of infection seems probable, or at the very latest these studies should be started with the earliest signs of infection. With this information at hand, at the time of the development of a critical condition, the clinician is much better able to decide whether or not specific chemotherapy is indicated without an objectionable loss of time. An example of the application of this principle might be cited, such as taking of vaginal swabs for culture during long labors, at the time of a delivery which is unduly difficult, when completing an incomplete abortion, in patients with recent upper respiratory infections, or at other times when later difficulties seem probable or even possible. It may be well to point out at this time, that it is usually possible to arrive at a probable diagnosis of the presence of hemolytic streptococci in such material, in from five to seven hours and a positive diagnosis in about sixteen hours. It is also of great importance to have frequent bacteriologic investigations after the institution of chemotherapy, to correlate with the clinical course of the disease, for the control of treatment.

Sulfanilamide was the drug used in all patients in this study, excepting those with pneumonia, where sulfapyridine was employed. I have not been greatly impressed with the claimed advantages of other preparations such as prontosil, neoprontosil, benzyl sulfanilamide, sulfanilyl sulfanilamide, etc., over sulfanilamide. Alyea,¹ however, has recently reported the successful employment of sulfanilyl sulfanilamide in a group of male patients with gonorrhea who had failed to respond previously to sulfanilamide. Most German investigators appear to prefer this drug, or those closely allied to it, such as sulfanilyl dimethyl sulfanilamide, in the treatment of gonorrhea. Their results, however, are in general not as good as those here reported. Accordingly, it appears advisable for the present, to utilize only the two preparations mentioned and evaluate the results as thoroughly as possible before proceeding with the use of other related compounds.

It will be noted that the dosage employed is quite varied. In many instances in urinary tract infections, we have employed a low dosage method as first advocated by Kenny and others.² In other cases a much larger dosage has been used either experimentally or because control bacteriologic studies failed to indicate a satisfactory result. Where prac-

tical, the dosage has been decreased or stopped before the patient received relatively high or protracted dosage. The avoidance of serious toxic manifestations, particularly agranulocytosis, appears to be largely possible by not unnecessarily prolonging the treatment or by not giving too high dosage. The discontinuance of the drug with the development of "drug fever" is usually indicated. Colebrook³ very recently reviewed 41 reported cases of agranulocytosis. It is significant that the average dose of the drug in these cases was 48 gm. and in only two cases was the total dosage less than 30 gm. Other observations of importance were the facts that the average duration of treatment was twenty days and that many of the victims were those that received repeated courses of therapy. These considerations may well be borne in mind, especially when treating conditions that are not likely to lead to a fatal outcome. At the same time adequate dosage to maintain a satisfactory blood level or urine concentration must be maintained for a prompt therapeutic response.

In pregnant women at term, sulfanilamide, owing to its marked diffusibility, has been shown by Speert⁹ to pass the placenta and invade the fetus in concentrations relatively similar to that of the maternal organism. As far as I am aware no untoward effect on the infant has so far been reported. Speert, in a recent experimental study, found a deleterious effect on the offspring of rats where the mother was given the drug throughout pregnancy. Maternal milk also contains the drug in concentrations considerably higher than the blood, but again no untoward toxic signs or symptoms in the nursing infant have been reported.

In the analysis to follow it will be noted that no mention is made of the use of the drug prophylactically in obstetrics, in an attempt to reduce the incidence of intra-partum or puerperal infection. Such use under certain conditions has been suggested by LaComme,²¹ Colebrook,⁴ Merlin,⁵ Johnstone,⁶ Hoare⁷ and others. As I have previously shown,⁸ less than 1 per cent of puerperal infection in our service is due to the beta hemolytic streptococcus, and only between 2 and 3 per cent is due to a beta strain. In other words, considerably less than one patient out of every 1,000 is likely to develop a beta hemolytic streptococcus infection. This small incidence, to my mind, does not warrant the routine prophylactic use of the drug. There may occasionally be circumstances surrounding a given patient, such as a recent hemolytic streptococcus infection, or the patient has been in contact with such infections. Then the prophylactic use of the drug may be indicated. There has been, however, no work as yet that proves conclusively the value of the drug when given prophylactically.

The present study is based on an analysis of 180 patients treated during the past three years in the New York Lying-in Hospital. The majority of the patients, however, were cared for during the past one and one-half years. The relative importance of the various indications for the use of the drug may be judged by an analysis of the clinical material herein reported. There were 115 patients with urinary tract

infections, 86 of whom were obstetric, and 29 gynecologic; 34 patients had gonorrhea, 20 puerperal or postabortal infections, 7 pneumonia, and 4 miscellaneous infections. Included in this latter group, there are one case of lymphogranuloma venereum and one patient with subacute bacterial endocarditis. We have not had an opportunity of evaluating the results in gonorrheal ophthalmia in the newborn, Welch's bacillus infections, or in chaneroid disease. It may be of interest to know that well over 2,000 specimens were studied in our bacteriologic laboratory, for the diagnosis and control of treatment, in the cases here reported.

All patients were treated in the Hospital as bed patients, with the exception of a few with chronic urinary tract infection who were treated by means of one or more courses of small dosage, consisting of 1.5 gm. per day for five days, while attending the Out-Patient Department. Unless some reason to the contrary existed, all medication in the hospital was given at four-hour intervals, both by day and by night, combined with an equal amount of sodium bicarbonate. Blood hemoglobin estimations and the white blood count were done on all hospital patients at least every second day. The drug concentration in the blood, and the urine if indicated, was done at similar intervals. An attempt was made to control the fluid intake, unless contraindicated by fever, so that the urinary output would approximate 1,000 c.c. per day. No dietary restrictions were employed. Nicotinic acid, as advocated by McGinity,¹⁰ was used with some apparent success in a number of our recent cases in an attempt to eliminate some of the minor toxic symptoms. Consideration of the efficiency of renal function was a preliminary prerequisite to therapy. As far as I am aware, renal insufficiency or anemia never deterred us from giving the drug. Other necessary medication was used when indicated. Transfusions were not deferred if thought advisable.

A description of the laboratory procedures employed is omitted for purposes of brevity. Suffice it to say that the studies were instituted as soon as possible after the material was obtained, and every effort was made to identify promptly and accurately the organisms associated with any given infection.

URINARY TRACT INFECTIONS

Tables I to XI are self-explanatory. The clinical and laboratory data in each group of patients as well as results of treatment are clearly shown. The results of sulfanilamide determinations in the blood and urine are not included in the tables. In general where "small" dosage

TABLE I. BACILLURIA* OF PREGNANCY (SULFANILAMIDE THERAPY)

Ante partum		13
Previous urinary tract infection	6	
Urinary tract symptoms	7	
Post partum		44
Previous urinary tract infection	12	
Urinary tract symptoms	32	
Total		57

*Pus in urine and positive culture but not necessarily febrile.
455 cultures studied, an average of 8 per patient, variation 2-24.

"2 gm. daily" was employed the blood level of free sulfanilamide was usually 2 to 4 mg. per cent and the urine concentration about 40 to 75 mg. per cent. Where the "medium" dosage was used the figures were 5 to 7 mg. per cent in the blood and 100 to 150 mg. per cent in the urine. The concentrations in the blood with "large" dosage varied from 7 to 15 mg. per cent and in the urine from 200 to 400 mg. per cent. This information in addition to frequent bacteriologic studies of the urine are essential for the intelligent and successful treatment of patients with this disease.

TABLE II. BACILLURIA* OF PREGNANCY.

Results of Treatment

ORGANISM		DRUG CURE†	FINAL CURE‡	LAST CULTURE STERILE
<i>Ante partum</i>				
<i>B. coli</i>	10	10	9	4
<i>B. coli</i> + <i>B. aerogenes</i>	2	2	1	1
Strept. (nonhem.)	1	0	0	0
<i>Post partum</i>				
<i>B. coli</i>	32	28	24	12
<i>B. coli</i> + <i>B. aerogenes</i>	7	4	4	3
(hemolytic)	2	0	1	1
Strept. (nonhem.)	2	1	1	1
Staph. (albus)	1	1	1	1
Total	57	46 (81%)	41 (72%)	23 (40%)

*See footnote Table I.

†Drug cure, causative organism disappeared from urine during therapy. It may, however, have reappeared in later specimens.

‡Final cure, causative organism not present in final specimens. (Usually 3 in number.) Streptococcus, staphylococcus, or diphtheroids may be present in either group.

TABLE III. BACILLURIA* OF PREGNANCY. CORRELATION OF DOSAGE TO "CURE"

DOSAGE	COURSES	"DRUG" CURE†	"FINAL" CURE‡	LAST CULTURE STERILE
Small (1.5-2 gm. daily)	1	20	20	11
	2	9	8	5
	3	4	4	1
	4	1	1	1
Medium (2-4 gm. daily)	1	3	3	2
	3	1	0	0
Large (4-7 gm. daily)	1	6	5	3
	1 + 8 ^s	2	0	0
Total		46 (81%)	41 (72%)	23 (40%)

*See footnote Table I.

††See footnotes, Table II.

TABLE IV. PYELITIS* OF PREGNANCY. CLINICAL DATA

Mild: 8	Moderate: 13	Severe: 8
11 Bilateral		
7 Right		
11 Unknown (mostly right ?)		
15 Ante partum (onset 1-125 days before delivery)		
14 Post partum (onset 1-150 days after delivery)		
Febrile course 2-17 days. Temperature normal before starting drug in 7 cases. At least 6 had nitrogenous retention in blood.		
Follow-up studies averaged 4 months		

*Includes pyeloureteritis and pyelonephritis.

The results in general when analyzed are not quite as successful as anticipated. In the first place, our criteria of cure by the last culture being sterile is often vitiated by the presence of a *Staph. albus* or diphtheroids which are for the most part probably contaminations. In

TABLE V. PYELITIS* OF PREGNANCY. BACTERIOLOGIC STUDIES

Specimens cultured	228
Average per patient	8
Variation	2-16
<i>B. coli</i>	21 patients
<i>B. aerogenes</i>	4 patients
<i>B. coli</i> and <i>B. aerogenes</i>	1 patient
<i>Staph. aureus</i>	2 patients
<i>Streptococcus</i> (beta hem.)	1 patient
Some of the following organisms were present on one or more occasions in all but 5 cases	
<i>Strept. nonhemolytic</i>	19
<i>Staph. albus</i>	12
Diphtheroids	7
<i>B. aerogenes</i>	4
<i>B. coli</i>	2
<i>Chromobacterium</i>	2

*See footnote Table IV.

TABLE VI. PYELITIS* OF PREGNANCY. CORRELATION OF TYPE OF INFECTION AND DOSAGE TO RESULTS

ORGANISM		DOSAGE	DRUG "CURE"†	FINAL "CURE"‡	LAST CULTURE STERILE
<i>B. coli</i>	10	"Small" (2 gm. daily)	7	7	7
<i>B. aerogenes</i>	3	"Small" (2 gm. daily)	2	2	2
<i>B. coli</i> and <i>B. aerogenes</i>	1	"Small" (2 gm. daily)	0	1	1
<i>Strept. (hemolytic)</i>	1	"Small" (2 gm. daily)	0	0	0
<i>Staph. aureus</i>	1	"Small" (2 gm. daily)	1	1	1
<i>B. coli</i>	5	"Large" (over 4 gm. daily)	4	3	1
<i>Staph. aureus</i>	1	"Large" (over 4 gm. daily)	0	0	0
<i>B. coli</i>	6	"Large" + "Small"	0	5	3
<i>B. aerogenes</i>	1	"Large" + "Small"	1	1	1
Total	29		15 (52%)	20 (69%)	16 (55%)

*See footnote Table IV.

†‡See footnotes, Table II.

TABLE VII. BACILLURIA* IN GYNECOLOGY. CLINICAL DATA 18 PATIENTS

Type of Operation:	
Plastic repair	10
Laparotomy	1
Insertion of stem pessary	1
Nonoperative	6
Type of Infection:	
<i>B. coli</i>	12
<i>B. aerogenes</i>	5
<i>B. proteus</i>	1
Number of specimens cultured 83, average 4.6 per patient.	

*Cystitis, chronic infection, urinary tract symptoms, or in a few cases prophylactic use of the drug.

TABLE VIII. BACILLURIA* IN GYNECOLOGY. DOSAGE OF SULFANILAMIDE AND RESULTS

ORGANISM		DOSAGE	DRUG CURE†	FINAL CURE‡	LAST CULTURE STERILE
<i>B. coli</i>	9	Small (1.5-2 gm daily)	7	8	6
<i>B. coli</i>	2	Medium (2-4 gm. daily)	1	1	0
<i>B. coli</i>	1	Large (4-6 gm. daily)	1	1	0
<i>B. aerogenes</i>	5	Small (1.5-2 gm. daily)	1	1	0
<i>B. proteus</i>	1	Medium (2-4 gm. daily)	0	0	0
Total	18		10 (56%)	11 (61%)	6 (33%)

Four patients had other forms of therapy, bladder irrigations, etc. Follow-up incomplete in 8 cases

*See footnote Table VII.

†‡See footnotes, Table II.

TABLE IX. PYELITIS IN GYNECOLOGY. CLINICAL DATA 11 PATIENTS

Mild: 5	Moderate: 5	Severe: 1
Febrile course 3 to 10 days, average 6 days		
Fever subsided before sulfanilamide therapy 1 patient		
Type of operation:		
Plastic repair		7
Laparotomy		3
Nonoperative		1
Type of infection:		
<i>B. coli</i>		9
<i>B. coli</i> and <i>B. aerogenes</i>		1
<i>B. aerogenes</i>		1
Number of specimens cultured 52, average 4.7 per patient		

TABLE X. PYELITIS IN GYNECOLOGY. DOSAGE OF SULFANILAMIDE AND RESULTS

ORGANISM		DOSAGE	DRUG CURE*	FINAL CURE*	LAST CULTURE STERILE
<i>B. coli</i>	3	Small 1.5-2 gm. daily	1	3	2
<i>B. coli</i>	2	Medium 2-4 gm. daily	0	0	0
<i>B. coli</i>	4	Large 4-6 gm. daily	2	3	2
<i>B. coli</i> and <i>B. aerogenes</i>	1	Medium 2-4 gm. daily	0	0	0
<i>B. aerogenes</i>	1	Large 4-6 gm. daily	1	1	1
Total	11		4 (36%)	7 (64%)	5 (45%)

Variation of sulfanilamide determinations (Urine 46-333 mg. %)
(Blood 4-16.1 mg. %)

Largest decrease in Hg during therapy—14%.

Drug fever in 2 patients.

*See footnotes, †‡ Table II.

TABLE XI. SUMMARY. URINARY TRACT INFECTIONS

GROUP	NUMBER OF PATIENTS	DRUG CURE*	FINAL CURE*	LAST CULTURE STERILE
Obs. Bacilluria	57	46 (81%)	41 (72%)	23 (40%)
Obs. Pyelitis	29	15 (52%)	20 (69%)	16 (55%)
Gyn. Bacilluria	18	10 (56%)	11 (61%)	6 (33%)
Gyn. Pyelitis	11	4 (36%)	7 (64%)	5 (45%)
Total	115	75 (65%)	79 (69%)	50 (43%)

Total cultures studied 818

*See footnotes, †‡ Table II.

many, although not all instances, the same may apply to cocci included in the nonhemolytic streptococcus group. When we have carried out quantitative tests, the total number of these organisms present has frequently been very small. If, however, these organisms appear repeatedly, they are, I believe, indicative of a low grade chronic infection. In such instances it is not uncommon for the *B. coli* to reappear in the urine at a later date, sometimes months after the sulfanilamide therapy. Accordingly, therefore, patients designated as having "final cure" as shown in the various tables, probably represent the best index of the favorable results. If our findings were calculated from the microscopic examination of stained urinary sediment, I am sure the cure rate would be very definitely increased. Again our failures sometimes occurred in patients with incomplete follow-up study and treatment.

We have not been able to duplicate the excellent results obtained by Kenny,² who advised relatively small dosage (1.5 to 1.8 gm. daily for five to seven days), by the use of either small or large dosage. Since Kenny's report, Cuthbert¹¹ has reported further experiences on urinary tract infections in the puerperium from the same hospital. He used a somewhat larger dosage, i.e., 2.25 to 3 gm. per day. His results are decidedly better than ours, but his follow-up observations are quite inadequate and accordingly vitiate his results to some extent. In the evaluation of results in obstetric and gynecologic urinary tract infections, the following fundamental considerations must be kept constantly in mind.

1. Gram-negative bacilli are foreign to the urinary tract of healthy gravid and nongravid women. Accordingly, our responsibility to the patient is not completed until we are assured that these organisms are not present in the urine.

2. The employment of cultural methods for the diagnosis of bacteria in the urine is far superior to reliance solely on the stained sediment.

3. Infection during pregnancy or the puerperium develops primarily because of anatomic and physiologic changes in the tract, because of congenital abnormalities, or because of trauma which is most frequently associated with labor and delivery. In gynecology these infections frequently occur as a result of anatomic or pathologic changes adjacent to the urinary tract or as a result of operative procedures.

4. The infecting organism is a gram-negative bacillus in over 90 per cent of the cases (106 out of 115 in the present study).

5. Bacilluria developing during pregnancy or the puerperium does not necessarily represent tissue invasion or actual infection. At the same time it is always the precursor of infection and accordingly infection frequently follows bacilluria.

6. Spontaneous disappearance of gram-negative bacilli from the urinary tract, when associated with infection, rarely ever occurs during pregnancy, but not infrequently happens after delivery.

7. The treatment of urinary tract infections "par excellence" is the immediate termination of pregnancy. Crabtree¹² has reported a spontaneous cure rate of 66 per cent by the fourth month post partum in a series of 44 patients with bacilluria. McLane²² found in a group of

71 ante-partum patients not treated with sulfanilamide, who had pyelitis, that *B. coli* was eliminated from the urine in 47 or 66 per cent in from eleven days to three years. One of the earliest spontaneous cures with which I am acquainted occurred in a patient of ours with a severe ante-partum pyelitis who had fever for twenty-four days prior to delivery. The urine culture revealed *B. coli* three days before delivery. She had negative cultures for *B. coli* from the bladder, right and left kidneys on the thirteenth day of the puerperium without any special therapy after delivery.

Bearing these facts in mind great caution must be exercised in drawing conclusions. We are, however, very much impressed with several observations. First, the longer the infection is present the more difficult is its eradication. Second, that sulfanilamide therapy *per se* may sterilize the urine but, in the presence of strictures or fibrosis of the ureter, the infection often returns after a course of treatment. Third, the use of intravenous pyelograms and cystoscopy for diagnostic purposes is essential, especially in instances where the infection fails to respond or a positive culture recurs after ceasing the medication. The number of cystoscopic examinations can, however, be greatly reduced. In the fourth place the elimination of *B. coli* in the ante-partum group, as shown in Table IV, is of fundamental importance. This is not a coincidence and suggests a most effective method of preventing the more serious urinary tract infections. The average duration of the febrile phase of the disease, in the 40 patients with pyelitis, was six days. The drug was not started until after the temperature returned to normal in 8 cases, while in the additional cases, especially during our early experience, it was not started until sometime after the onset of the febrile reaction. Traut²⁷ found a decrease of approximately 50 per cent in the length of the febrile reaction in sulfanilamide treated patients, as compared to a group that were not treated by this drug.

A study of all the "final cure" failures, 36 in number, suggests that 26 are largely due to inadequate dosage or incomplete follow-up. Another five were in-patients with long-standing urinary tract infections. Other unknown factors also must have played some role in these failures. Accordingly it appears that most urinary tract infections will respond to adequate sulfanilamide therapy. The earlier and milder the infection in question the better the response will be. Long-standing and severe infections usually necessitate larger dosage. In general if the patient does not respond to such therapy one should think of parenchymal involvement of the kidney, perirenal infection, or extraurinary tract disease.

GONORRHEA

Tables XII to XIX summarize the clinical and laboratory data relative to 34 patients who had gonorrhea. We are indebted to the New York Department of Health for referring many of these patients to us for treatment.

The results of treatment in gonorrhea have been very dramatic. The discharge and other clinical symptoms disappear very promptly. Early in our study we treated three patients with relatively small dosage

TABLE XII. GONORRHEA. CLINICAL DATA

AGE	PATIENTS
15-20	10
21-25	8
26-30	5
31-35	6
36-40	5
Total	34
Race	
White	26 (76.5%)
Black	8 (23.5%)
Married	15
Single	14
Divorced	5

TABLE XIII. GONORRHEA. CLINICAL DATA

PREVIOUS PREGNANCIES	PATIENTS
0	18
1	11
2	3
4	2
4 treated during pregnancy	
1 treated during puerperium	
1 conceived and delivered since therapy.	
Acute initial infection	21
Exacerbation or reinfection	13
Lower genital tract infection	17
Lower and upper genital tract infection	17
Arthritis (elbow)	1
Fever, average duration 6 days (due to disease)	11

TABLE XIV. GONORRHEA. CLINICAL DATA

DURATION OF SYMPTOMS	PATIENTS
None	5
Less than 7 days	4
1-4 weeks	14
1-3 months	8
3-12 months	3
Interval between diagnosis and treatment	
0-7 days	24
8-24 days	7
35-80 days	3

TABLE XV. GONORRHEA. INITIAL BACTERIOLOGIC STUDY*

Cervical cultures positive	31
Cervical smears positive	17
Cervical smears extracellular forms only	8
Urethral cultures positive	22
Urethral smears positive	8
Urethral smears extracellular forms only	3

*32 patients where both culture and smear were taken before therapy.

TABLE XVI. GONORRHEA. CONTROL BACTERIOLOGIC STUDIES

Positive cultures	88
Negative cultures	457
Unsatisfactory cultures	2
Total	547
Average per patient	16
Positive smears	45
Extracellular forms only	28
Negative smears	455
Total	528
Average per patient	15.5
Total Specimens Studied	1075

TABLE XVII. GONORRHEA. SULFANILAMIDE TREATMENT*

Approx. average daily dose	4.9 gm.
Approx. average duration of therapy	7.3 days
Approx. average total dose	36.9 gm.
3 patients received 2 of above courses of therapy	
2 for exacerbation or reinfection	
1 Pelvic inflammatory disease with masses for evaluation	
Cure—negative cultures and smears established in all cases. Two patients readmitted 15-30 days after discharge with exacerbation or reinfection.	

*All patients hospitalized 8 to 34 days (av. 13.8 days). (3 patients treated prior to admission, daily dose 1.5-3.6 gm. for 7 days. Total dosage average 20 gm. All failures.)

TABLE XVIII. GONORRHEA. FOLLOW-UP

1-16 months. Average per patient 3.06 mo.
 Inadequate follow-up, i.e., less than 2 months, 7 patients
 Average cultures and smears per patient 16

Toxic Symptoms

None	12 patients
Headache	15 patients
Cyanosis	11 patients
Dizziness	11 patients
Nausea	11 patients
Fever	9 patients
Vomiting	3 patients
Anorexia	3 patients
Rash	2 patients
Palpitation	1 patient

Note: Several patients received nicotinic acid to relieve symptoms or prophylactically.

TABLE XIX. GONORRHEA. BLOOD OBSERVATIONS

	PATIENTS
W.B.C. count over 10,000 on admission	18
Lowest W.B.C. count recorded 6,000	
W.B.C. count increased during therapy in	7
W.B.C. count over 10,000 on discharge in	9
Highest W.B.C. count on discharge 12,600	
Hemoglobin per cent decreased in	20 (58%)
Hemoglobin per cent decreased more than 10% in	8 (24%)
Hemoglobin per cent decreased more than 20% in	2 (6%)
Largest decrease in hemoglobin 28%	
Blood sulfanilamide over 10 mg. % in 8 patients (24%). Only one patient failed to reach a blood concentration of 5 mg. %.	

(1.5 to 3.6 gm. daily) for five to seven days per course. The rapid subsidence of the clinical symptoms was very encouraging; however, cultures and sometimes smears continued to be positive. This suggests a possible danger in that patients receiving as much as 20 gm. of sulfanilamide during one week in an ambulatory state may show marked clinical improvement and even negative smears, yet they are possible serious sources of infection. Bomze²³ has recently reported his experience treating 45 ambulatory patients with approximately 2.6 gm. per day in courses of five days' duration. This makes about 13 gm. per course. He reports only one failure, but 14 recurrences, which he attributes to reinfection. In view of our early but limited experience with ambulatory patients, and the fact that his study apparently is based on smears without cultures it would seem possible that he may be erroneous in attributing all his recurrences to reinfection.

Following our early experience, it became evident that considerably larger dosage was necessary. Since that time, all patients treated have been hospitalized and kept in bed during their entire treatment. Under these conditions the drug is tolerated much better, toxic symptoms are detected as they appear, and laboratory facilities can be utilized to the fullest extent. In addition to these advantages under this system of treatment, we have not had a single instance of an extension of the infection from the lower to the upper genital tract. It was previously noted that nine of the 34 patients developed drug fever. This and the previously cited reasons make me feel very strongly that this disease in the female should not be treated by sulfanilamide in ambulatory patients.

It appears to be unusual to diagnose and treat women during the early days of the disease. Only four of our patients gave a history of symptoms of less than seven days' duration. Another five cases gave no symptoms, being discovered by contact studies, but probably had, more or less, long-standing infections. Accordingly, the important observation, made by many authorities treating male patients, that the acute cases do not respond as favorably as the chronic infections, probably is not of great importance in the treatment of this disease in the female.

This study very clearly demonstrates the superiority of cultural methods over smears for the diagnosis and control of treatment in gonorrhea. Occasionally, the smears will be positive for extracellular forms only and the cultures negative, however, the reverse is very much more often the case. Carpenter and others¹⁹ in a recent statistical analysis of diagnostic methods found the cultural method 191 per cent superior to the smear method.

The dosage varied from 4.2 to 6 gm. daily, an average of 4.9 gm. This was calculated on a basis of 1 gm. of the drug to each 20 to 25 pounds of body weight. The duration of treatment varied from five to eleven days, but in most cases the drug was prescribed over seven consecutive days. No other form of treatment was prescribed. Cure of the lower genital tract infection by repeated cultures and smears was established in all patients before discharge. Two single delinquent

irresponsible colored girls in the second decade of life, one of whom was pregnant, were found to have negative cultures and smears at the time of their first follow-up examination after discharge, but both were positive when they returned for their second examination. One gave a history of repeated exposures during the interval, while the other denied such experiences. Both have been readmitted and re-treated and again their cultures and smears became negative and have remained so to date. Whether these two cases, represent an exacerbation of the original infection or a reinfection, I cannot say. In any event the other 32 patients have shown no evidence of recurrence or reinfection.

The dramatic results obtained can be realized when on analysis, we found that in 26 patients no positive culture or smear was obtained after starting treatment. In the remaining 8 patients, the laboratory diagnosis became negative in from one to five days and only 2 patients were in the five-day group. As previously stated smears and cultures were usually taken at two-day intervals during hospitalization. In a very recently treated patient not included in the present series where specimens were examined every four hours, the urethral culture was found to be negative in eleven hours and the cervix in twenty-four hours after the institution of treatment. Rare pleomorphic extracellular forms were occasionally found in the cervical smear for the following two days.

It has not been our experience that sizable thick-walled pelvic masses were in any way affected by the sulfanilamide therapy. This is contrary to the experience of J. H. Long, as quoted by Long and Bliss¹⁶ and Grodberg and Carey²⁰ and others who found a decrease in size, resolution, or disappearance of the masses. However, acute or subacute salpingitis of specific origin, not complicated by secondary infection, has in our experience responded well to the drug. Recently, in several patients with sizable pelvic masses, we have employed "nonspecific" fever therapy after completion of the sulfanilamide treatment. No conclusions can as yet be drawn from these few patients.

If we count the two above mentioned cases as failures, which seems dubious, our cure rate by the criteria employed is 94 per cent. Figures in the literature vary from about 30 to 95 per cent. However, there is great variation in daily dosage and total duration of treatment. In 312 female patients reported by four different authors the average cure rate was 65 per cent. As many of the patients in this composite series were controlled only by smear the results cannot be regarded as being entirely reliable. Mahoney²⁴ has recently reported a comparable series to the here reported cases. The patients were all hospitalized, he employed large dosage, and they were all controlled by both smear and culture. It is interesting to note that according to his criteria 93.4 per cent were cured.

The results then are very superior, if the patients are properly treated, to any of the older forms of therapy such as, the application of local antiseptic substances, local heat, nonspecific protein injections, serums, vaccines or specific fever therapy. It appears probable that about one-fourth of the million patients who are infected annually in

this country, with this disease, are women. As this incidence is greater than that of any other communicable disease, the responsibility of the gynecologist and obstetrician is obvious.

I am convinced from my experience in treating patients with gonorrhea that:

1. The original diagnostic procedure and all follow-up examinations should include cultures as well as smears.
2. Adequate dosage (5 to 6 gm. daily) for about seven days is necessary for the successful treatment of the disease.
3. Cure is effected during the first forty-eight hours of therapy in the majority of patients, but occasionally it takes at least five days.
4. Gradually decreasing dosage of the drug is not indicated following the initial "high" dosage.
5. Hospitalization is essential for the satisfactory and safe employment of sulfanilamide.
6. Haphazard treatment with inadequate dosage often renders the patient asymptomatic. Such individuals may be a serious menace to society by spreading the disease, in addition to bringing discredit to this form of therapy.

PUERPERAL INFECTION

It was on this subject that Colebrook published his first observations in the *Lancet* of June 6, 1936. This was unquestionably of great importance in stimulating interest in the English-speaking world in these compounds. It is unfortunate that many of the subsequent contributions, by other authors, have failed to include accurate bacteriologic diagnoses and accordingly add but little to our knowledge. Our experience, it is true, is small, being limited to 20 cases. In a considerable number of these patients the drug was employed under carefully controlled conditions in order to evaluate results in the presence of different infecting organisms. However, our experience has been somewhat broader than is indicated in the puerperal infection group, because two-thirds of the patients reported with post-partum bacilluria had a febrile puerperium, and obviously in many cases the febrile reaction was due to genital tract infection. Cultures were obtained from the lochia in these patients. Tables XX and XXI summarize the results.

Definite therapeutic effects were obtained only on those patients with hemolytic streptococcus infections. Two of the 8 patients in this group

TABLE XX. PUERPERAL AND POSTABORTAL INFECTION. CLINICAL DATA

20 patients with moderate to severe infection. Fever 3 to 35 days. Average duration 11 days		
16 puerperal infection		
4 postabortal infection		
PATIENTS	BLOOD CULTURE POS.	INFECTING ORGANISM (UTERINE CULTURE)
8	2	Hemolytic strept. (beta)
8	2	Anaerobic nonhem. strept.
1	1	<i>Strept. viridans</i>
2	0	Aerobic nonhem. strept.
1	0	<i>B. coli</i> and <i>B. aerogenes</i>

TABLE XXI. PUERPERAL AND POSTABORTAL INFECTIONS.
TREATMENT (SULFANILAMIDE)—RESULTS

PATIENTS	DAILY DOSE	TOTAL DOSE
2	1.5 gm.	13.5-15 gm.
18	4-6 gm.	20-45 gm.
Clinical course modified by drug in,		
2* Hemolytic streptococcus infections		
1 Anaerobic streptococcus infection (also urinary tract infection)		
1 Anaerobic streptococcus infection (? effect)		
1 <i>Strept. viridans</i> infection (discharged with pelvic mass)		

*The hemolytic streptococcus disappeared from the vaginal secretions in from five to twenty-three days in the six other cases.

had positive blood cultures but they were not severely ill patients. In fact all 8 patients may have recovered without sulfanilamide. There was suggestive evidence of response in 3 other cases but, as Table XXI shows, the findings are not clear-cut. I have yet to see conclusive evidence of a favorable response in puerperal infection where the infection is due to organisms other than the hemolytic streptococcus. Colebrook,¹³ although his reported clinical experience with other types of puerperal infection is small, is of the same opinion. In a recent report by Morris,¹⁴ we are not informed of the bacteriologic findings, and despite the fact that he has treated 97 cases of puerperal and postabortal infection with more than an equal number of controls, his findings are of no value, to my mind, in drawing conclusions, other than the broad statement that there is little response to this form of treatment in post-partum or puerperal infection in general. It is of the utmost value as far as the welfare of the patient is concerned to have accurate information concerning the nature of the infecting organisms. I must completely disapprove of Long's¹⁵ advice in his recent monograph, namely, "that the chances of a given puerperal infection being hemolytic streptococcal in origin are overwhelming, and hence, sulfanilamide should always be prescribed at the first sign of the disease." Long¹⁵ has wrongly drawn his conclusions as to incidence of the hemolytic streptococcus in puerperal infection from the work of Colebrook and Purdie¹³ who were reporting primarily only on hemolytic streptococcus infections treated with sulfanilamide. Quite naturally then, the latter authorities reported 100 instances of hemolytic streptococcus infection and an additional 6 cases, 3 of whom were staphylococcus infections and the other 3 anaerobic streptococcus infections. In the latter group there was no definite therapeutic effect noted. As I have previously pointed out, the incidence of beta hemolytic streptococcus infections is so low in proportion to those caused by other organisms which, as far as we know, are for the most part not affected by the drug, that to give all patients with puerperal infection sulfanilamide would be in direct contrast to the best interests of the patient. Bacteriologic investigation of the nature of the infection, if not already under way should certainly be started coincident with "the first sign of the disease."

To summarize our information concerning the indications for the use of sulfanilamide in puerperal infection, we may make the following

statements: It is usually indicated in hemolytic streptococcus infections especially if the patient is ill. I say "usually," advisedly, because most hemolytic streptococcus infections during the puerperium are local in extent and recovery, without any serious sequelae, occurred in about 95 per cent of cases before the advent of these new drugs. Present-day knowledge, it is true, implies that many of these infections were probably caused by organisms belonging to groups other than Group A (Lancefield). If there is an associated septicemia, peritonitis, or other evidence of spread of the infection, the drug should be started early, the dosage should be high and determinations of the concentration of the drug in the blood made frequently. In such cases a concentration of at least 10 mg. per cent should be maintained. Repeated blood cultures serve as an excellent guide during the critical period of illness. In anaerobic and aerobic nonhemolytic streptococcus infections, there is no evidence that the drug will in any way alter the clinical course of the disease. There is no evidence of which I am aware, to show that the drug affects infections in the genital tract with organisms of the colon aerogenes group. Recently, Sadusk¹⁷ following the work of Bohlman¹⁸ has reported the successful treatment of a *B. welchii* infection in two cases of postabortal infection with positive blood cultures. Serious infections with this organism although infrequent have always in the past produced a high mortality. Accordingly, if possible, they should be diagnosed early and treated with large dosage when encountered. Other supportive forms of therapy including transfusions should be used as well as the sulfanilamide in our therapy.

The pneumonia group of patients are shown only to complete the picture. In general, the results are most dramatic. In such a serious complication, we are reluctant to rely entirely on sulfapyridine if an antiserum is available for the type of pneumococcus isolated. Early diagnosis and prompt treatment are essential to good results. I have summarized in Table XXII the pertinent data in relation to seven patients, all of whom recovered, who have been treated with sulfapyridine. It is interesting to note that on our obstetric service we have had an average of one death per year from pneumonia during the years 1932 to 1937, inclusive, while no deaths have occurred during the past two years. Such information is of course not statistically significant.

In the miscellaneous group it is gratifying to note the improvement in the patient with lymphogranuloma venereum. The dosage employed was relatively low (1.8 gm. daily) over a rather long period of time (twenty-two days) somewhat as suggested by Shropshear, whose results are quite stimulating. It is interesting to note that the blood stream became sterile following treatment, in the patient with the overwhelming hemolytic streptococcus infection. This patient subsequently died primarily because of the infection, although she did have a chorionepithelioma with early lung metastases. Table XXIII presents the pertinent data.

TABLE XXII. PNEUMONIA—(SULFAPYRIDINE)

STATUS	ORGANISM	DOSAGE	RESULT
1 Antepartum	Pneum. Type I	33.0 gm. + serum	Dramatic response
1 Postpartum	Pneum. Type I	44.0 gm. + serum	Dramatic response
1 Antepartum	Pneum. Type XVIII	22.5 gm.	Dramatic response
1 Postoperative	Pneum. Type I	19.0 gm.	Excellent response
1 Postoperative*	Pneum. Type III	67.0 gm.	Fair response
1 Antepartum	Pneum. not isolated	33.0 gm.	Excellent response
1 Postpartum	Pneum. not isolated	14.7 gm.	No response

*Developed nonhemolytic streptococcus blood stream infection from local operative site during high dosage of sulfapyridine. Sulfanilamide later with no effect.

TABLE XXIII. MISCELLANEOUS

DIAGNOSIS	DRUG	RESULT
1 Pelvic peritonitis followed Rubin's Test and Coagulation of cervix	Sulfanilamide 5 days (total dosage 21.6 gm.)	No response
1 lymphogranuloma venereum	Sulfanilamide 22 days (total dosage 40 gm.)	Remarkable improvement (also had local applications)
1 chorionepithelioma (admitted 2 months post partum)	Prontosil and prontolyn 7 days (1936) "adequate" dosage.	1. Blood culture 500 col. per c.c. 2. Blood culture 30 col. per c.c. 3. Blood culture 15 col. per c.c. 4. Blood culture no growth Died 9 days after admission
1 subacute bacterial endocarditis	Sulfanilamide 10 days (total dosage 32.4 gm.)	Blood culture <i>Strept. viridans</i> No response

CONCLUSIONS

General.—

1. Bacteriologic examinations of urine, blood, lochia, cervical and urethral secretions, etc., are of the greatest importance in the diagnosis, control and evaluation of chemotherapy in infections in obstetrics and gynecology.

Urinary Tract Infections.—

2. Organisms of the colon aerogenes group are the chief cause of urinary tract infections, complicating obstetric and gynecologic conditions. The urine under such circumstances can usually be rendered sterile with varying amounts of sulfanilamide. Subsequent follow-up is necessary because re-infection may recur if the same conditions subsequently exist as were present prior to the initial infection.

3. The urinary tract should be free from organisms before the patient is finally discharged. It is usually more difficult to render the urine sterile where the infection has been severe or has existed over a long period of time.

4. In ante-partum bacilluria and definite pyelitis, the urine was rendered bacilli-free and kept so in 10 of 13 cases. This fact is of great importance in the prevention of pyelitis. The earlier the diagnosis and treatment, the better the results will be.

5. The primary infecting organism was eliminated from the urinary tract in 69 per cent of a group of 115 obstetric and gynecologic patients with bacilluria or pyelitis, who were treated with sulfanilamide.

Gonorrhea.—

6. Employing relatively high dosage of sulfanilamide in hospitalized patients, for a relatively short period of time, gonorrhea in the female can probably be cured by the criteria of repeated cultures and smears in a large percentage of cases. The cure rate was at least 94 per cent in the 34 patients here reported.

7. For the successful and safe employment of sulfanilamide in the present state of our knowledge we are not justified in treating the disease by this means in ambulatory patients.

8. Cultures are essential for accurate diagnosis and are a much more reliable index of cure, than smears alone. However, the best results are obtained when both cultures and smears are employed.

Puerperal and Postabortal Infections.—

9. Prophylactic cultures should be taken where later infection appears probable.

10. Sulfanilamide is usually indicated in infections caused by hemolytic streptococci or *B. welchii*.

11. The drug is not known to exert any definite therapeutic effect in other types of infection.

REFERENCES

- (1) Alyea, Edwin P., and Daniel, Walter E.: *South. M. J.* 32: 608, 1939. (2) Kenny, M., Johnston, F. D., von Haebler, T., and Miles, A. A.: *Lancet* 2: 119, 1937.
- (3) Colebrook, Leonard: *Lancet*, p. 158, 1939. (4) *Idem*: *Ibid.* p. 286, 1939.
- (5) Merlin, Ludwig: *Schweiz. med. wchnschr.* 68: 1080, 1938. (6) Johnstone, R. W.: *Brit. M. J.* 1: 562, 1938. (7) Hoare, Edward, D.: *Lancet* 1: 76, 1938.
- (8) Douglas, R. Gordon: *Am. J. Surg.* 35: 352, 1937. (9) Speert, Harold: *Bull. Johns Hopkins Hosp.* 63: 337, 1938. (10) McGinity, A. P., Lewis, G. T., and Holtzclaw, M. R.: *J. M. A. Georgia* 28: 54, 1939. (11) Cuthbert, J. C.: *Lancet* 2: 720, 1938. (12) Crabtree, E. G., Prather, G. C., and Prien, E. L.: *AM. J. OBST. & GYNEC.* 34: 405, 1937. (13) Colebrook, Leonard, and Purdie, Anthony, W.: *Lancet* 2: 1237 and 1291, 1937. (14) Morris Theodore, J.: *AM. J. OBST. & GYNEC.* 38: 67, 1939. (15) Long, Perrin, H., and Bliss, Eleanor, A.: *The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds*, New York, 1939, The Macmillan Co., p. 174. (16) *Idem*: *Ibid.* p. 197, 1939. (17) Sadusk, Joseph, Jr., and Monahan, P., and Constantino, P.: *J. A. M. A.* 113: 14, 1939. (18) Bohlman, H. R.: *Ibid.* 109: 254, 1937. (19) Carpenter, C. M., Wilson, Karl M., and Leahy, Alice, D.: *Am. J. Syph. Gonorr. & Ven. Dis.* 22: 55, 1938. (20) Grodberg, B. C., and Carey, E. L.: *New England M. J.* 218: 1092, 1938. (21) LaComme: *Bull. Soc. d'obst. et de Gynéc.* 24: 443, 1936. (22) McLane: Personal communication. (23) Bomze, Edward, J., Fuerstner, Paul G., and Falls, Frederick, H.: *AM. J. OBST. & GYNEC.* 38: 73, 1939. (24) Mahoney, J. F., Van Slyke, C. J., and Thayer, J. D.: *Am. J. Syph. Gonorr. & Ven. Dis.* 22: 691, 1938. (25) Thompson, Luther: *Am. J. Clin. Path.* 5: 4, 1935. (26) McLeod, J. W., Coates, J. C., Hoppold, F. C., Priestley, D. P., and Wheatley, B.: *J. Path. & Bact.* 34: 221, 1934. (27) Traut, Herbert F.: Personal communication.

DISCUSSION

DR. REUBEN OTTENBERG—(By invitation).—In the genitourinary cases that I have had the opportunity to follow, the commonest cause of failure has been obstruction. If there is any remaining mechanical obstruction in the urinary tract, such as stone stricture, it will prevent a cure, or give a temporary apparent cure. Shortly after the drug is stopped, the same micro-organism will be found still infecting the tissues.

I wish to stress particularly the clinical toxicity of the drug. I do not refer to the minor effects, such as skin eruptions, cyanosis, the slight mental disturbance, dullness, and confusion that sometimes occur and which are not of serious import. I refer particularly to the grave, possibly fatal toxic results which must be classed as idiosyncrasies, which occur in human beings and not in animal experiments. No one knows how frequent they are; they probably do not add up to over 2 or 3 per cent of all cases. I am going to discuss particularly four serious complications: (1) acute hemolytic anemia; (2) jaundice; (3) agranulocytosis; and (4) urinary obstruction from sulfapyradine.

In the Johns Hopkins experience, as cited in the recent book of Long and Bliss, acute hemolytic anemia occurs in from 2 to 4 per cent of the cases. The condition is rarely fatal, although there have been two or three fatal cases reported in the literature. I have seen five typical severe cases, all of whom got well although two nearly died. Acute hemolytic anemia invariably occurs in the first three or four days of treatment, which has a very important bearing on the way that treatment should be started and watched by the physician. Most commonly there is a free period, i.e., one or two days of relative well-being between the onset of drug treatment and the appearance of symptoms. The two most severe cases that I have seen received the drug in small doses for one day only. In one instance the patient had 4 or 5 gm. of sulfanilamide in one day; the other received the same plus 20 c.c. of prontosil intramuscularly. There was a free interval of two days in both cases; on the third day they were suddenly markedly anemic, and vomited a material resembling coffee grounds. They also had diarrhea with coffee-ground appearance, intense hemoglobinuria, high fever, and mild jaundice. These two patients both developed marked oliguria, and one had suppression of urine for something over twenty-four hours. Both had marked retention of nitrogen in the blood. The therapy consisted of blood transfusion and large amounts of fluid parenterally.

The next complication I wish to discuss is jaundice, which is closely related to anemia. Jaundice usually occurs with acute hemolytic anemia, but there is a considerable number of cases in which jaundice occurs without it. When carefully studied by the usual method of liver function tests, those patients show unmistakable evidence of liver damage. I have seen seven such cases, but only three of them were very severe and only one of them died. That patient undoubtedly had acute yellow atrophy of the liver, although unfortunately no autopsy was obtained. This patient was a young man who was given sulfanilamide for mastoiditis, in the usual dosage. He developed a not very severe acute hemolytic anemia and the drug was stopped. The mastoiditis continued and he was given the drug again for a week. This was a mistake, because the drug should never be given again if the patient has developed acute hemolytic anemia (unless he has some probably fatal infection such as meningitis). There was a free interval of a week following this, after which he developed what looked like a mild jaundice. It got steadily worse and at the end of a month he died with all the symptoms of acute yellow atrophy of the liver.

Another patient with severe jaundice had apparently partially recovered. He was seen by me five months later and at that time he was still slightly jaundiced and had an enlarged spleen. He undoubtedly had developed chronic nodular sclerosis of the liver which, as you know, sometimes occurs after acute hepatic degeneration and which ultimately is likely to be fatal.

The third complication is agranulocytosis. I am not referring now to mild or moderate depression of the leucocyte count which probably never has any relation to acute agranulocytosis at all. The cases of agranulocytosis have not had this moderate depression, but instead the disappearance of granulocytes occurred suddenly, the leucocyte count previously having been over 5,000 per c. mm. and with the usual number of granulocytes. I have seen 5 cases of agranulocytosis, 4 of them fatal.

Agranulocytosis, unlike acute hemolytic anemia, does not occur in the beginning of therapy but only ten days or two weeks after. In most instances it occurs when very heavy dosage has been used over ten days or two weeks, although one patient that I saw received the drug for only one day, 6 gm. being given during

that time. It was a case which the initial diagnosis was streptococcus pneumonia because hemolytic streptococci were obtained from the sputum at the time of admission, and not pneumococci. Therefore, the patient was put on sulfanilamide for one day: on the second day pneumococci were found, serum was given and sulfanilamide was discontinued. The patient ran the usual course, and the pneumonia got better. But two weeks later when the patient was ready to be discharged from the hospital, he developed acute agranulocytosis with total disappearance of leucocytes from the blood and was dead in less than three days. In this case then there was a free interval. Apparently the moderate dosage of the drug for twenty-four hours only produced this result. Therefore, I do not think it is necessary to have prolonged, heavy dosage of the drug to produce agranulocytosis. It is the unexplained idiosyncrasy of the patient. The need for care in the use of the drug is obvious, but I am afraid that even constant watching of the leucocytes is of relatively little value in the prevention of agranulocytosis.

Four of the 5 patients with agranulocytosis that I have seen died. The patient that survived recovered after profuse transfusion therapy.

The complication, agranulocytosis may occur with either sulfanilamide or sulfapyridine. It is undoubtedly rare but perhaps not so rare as the published cases would lead one to think, for I keep hearing of unpublished cases.

The last complication is a new one and occurs only with sulfapyridine. It is the complication of hematuria due to a precipitate of acetylated sulfapyridine in the urinary tract. I have seen only two of those cases, one of them not a very severe hematuria, which subsided on the liberal administration of fluids. The other patient was a young man with acute bronchopneumonia, who was on sulfapyridine in the usual dosage. On the third day he developed an intense hematuria and in about forty-eight hours there was complete suppression of urine. In spite of every effort to get the kidneys to secrete again, it was impossible to do so and he died of uremia. A postmortem examination was done and amorphous deposits were found in the ureter and pelvis of the kidneys and in the tubules of the pyramids of the kidneys. Death was due therefore to mechanical obstruction. The only way we have to prevent such a condition is the liberal administration of fluids with the drug.

On account of these possible toxic effects I agree with the attitude of Dr. Douglas that these drugs must be used only in proved infections with micro-organisms that are potentially of serious import, that they must be used with great care, and that the patient, particularly in the first few days of treatment, must be under close daily supervision by his physician.

DR. ALBERT H. ALDRIDGE.—It is obvious that the most satisfactory results of treatment are likely if the types of bacteria causing the infections under treatment are known; if the twenty-four hour dose of the therapeutic agents to be used are determined according to body weight; if uniform concentrations of the drugs in the blood stream are maintained by regular four hourly administration of proper amounts of fluid as well as of the drugs being used and finally if the concentrations of the drugs in the blood stream are checked by one of the tests devised for the purpose.

In attempting to avoid the toxic effects of these new therapeutic agents, clinicians have probably often used doses too small to be effective. The results of careful pharmacologic and clinical studies such as those that have been presented will help to establish essential facts regarding effective doses, the seriousness of the toxic manifestations and the relative therapeutic value of these chemical agents as compared to former methods of treatment.

The value of sulfanilamide in the treatment of post-partum infections has been emphasized. In large series of patients with post-partum streptococcal infection treated at Queen Charlotte, Lane Roberts has reported a reduction in mortality from 22.5 to 5.3 per cent since sulfanilamide has been used. Sulfapyridine has become a valuable means of treating respiratory infections which occur after operation and in connection with pregnancy. Women who go into labor while suffering from acute respiratory infections not infrequently present serious problems for treatment in the post-partum period.

DR. RICHARD CHARLTON.—Dr. Douglas mentioned fever as a complication in the course of chemotherapy. In a case at the Lawrence Hospital, after eight days of 6 gm. daily doses of sulfanilamide given to control postabortal sepsis, the temperature reached 108.6° F. The drug was discontinued, and in forty-eight hours the temperature returned to normal. At the time when the elevation reached 108.6° F. the pulse rate was 200.

Dr. Marshall has made an important observation relating to possible deleterious effects of sulfanilamide on the fetus in utero. At the Lawrence Hospital, in the presence of infection late in pregnancy, we look upon sulfanilamide as contraindicated.

DR. EDWARD G. WATERS.—During 1937 and 1938 we had 19,830 deliveries with a morbidity from pelvic sepsis in 464 cases. Of that number, 50 patients were treated with sulfanilamide. Eleven patients had repeated positive blood cultures. Nine of these eleven were due to hemolytic streptococcus, one was due to the *B. coli*, and one to the *Streptococcus viridans*. Of this group of 11 patients we had two deaths, one of which was caused by the hemolytic streptococcus, and the other by the *Streptococcus viridans*.

Although 11 cases with a positive blood stream infection in a group of 53 patients with puerperal morbidity is a small series, nevertheless the results seem to me to be significant.

Dr. Douglas is to be commended for reiterating that with sulfanilamide treatment one should insure the patient against toxic complications by following the blood sulfanilamide level and carrying out a constant check on the white blood cell count, hemoglobin readings, etc.

OBSTETRIC FACTORS IN PREMATURE BIRTH*

ARMAND JEAN MAUZEY, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, University of Illinois, College of Medicine)

THE premature infant has been defined as an infant which weighs not less than 400 gm. nor more than 2,500 gm., measures in length not less than 28 cm. nor more than 48 cm., and is not less than twenty-two weeks in gestation nor more than thirty-seven weeks.

At the Research and Educational Hospitals of the University of Illinois College of Medicine, Department of Obstetrics and Gynecology, Chicago, from May 1, 1925, to March 1, 1939, there were 10,797 labors with subsequent childbirth in the In-patient and Out-patient Services. Of this number 765 labors were apparently premature. There were 50 twin births and two triplet births. A total of 819 premature infants therefore resulted from the 765 premature labors. There were 401 male infants born and 418 females.

A probable cause of prematurity was found in 434 labors. Of the probable causes three groups were recognized.

First in importance were those major single causes which accounted for 272 labors, namely, eclamptogenic toxemia, premature detachment of the placenta, syphilis, multiple pregnancy, habitual abortion, placenta previa, nephritic toxemia,

*Abridgment of Thesis submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Master of Medical Science (M.Sc. (Med.)) for graduate work in gynecology-obstetrics.

heart disease, and pyelitis. Second were those labors which were associated with more than one probable cause, totaling 102 labors and were in the main combinations of the major single causes, and finally a series of miscellaneous single causes of varying incidence and importance amounting to 60 labors.

Of the major single causes of prematurity eclamptogenic toxemia was seen most frequently. This complication was recognized when the blood pressure read 140/90 or over. The presence of albumin, a weight gain of five pounds or more in two weeks, stubborn edema, headaches, spots before the eyes, and dizziness were often additional signs. Twenty-five per cent of the premature labors having a probable single etiology were associated with this condition.

Premature detachment of the placenta was present in 38 instances. These cases did not always give the classical picture of premature separation. Lesser degrees of detachment were usually exhibited. Pain was not a common early symptom but bleeding was always present. Examination of the placenta following delivery revealed a portion sufficiently detached to produce premature labor. The term premature separation of a low lying placenta is more appropriate.

The presence of syphilis and multiple pregnancy followed in close order with 36 and 32 cases, respectively. The low incidence of syphilis as a probable cause of prematurity in our clinic may be explained by the fact that routine Wassermann and Kahn tests are done at the first prenatal visit and if found positive, antisyphilitic therapy is begun at once. A history of habitual abortion was present 15 times. Placenta previa was associated with prematurity in 14 cases. Nephritic toxemia was present in 13 labors. There were 10 instances of heart disease, while pyelitis was seen in combination with premature birth on only 6 occasions (Table I).

TABLE I. PROBABLE MAJOR SINGLE CAUSES OF PREMATUREITY
(Total Probable Known Causes 434)

	LABORS	PER CENT
Eclamptogenic toxemia	108	24.9
Premature detachment of placenta	38	8.7
Syphilis	36	8.3
Multiple pregnancy	32	7.3
Habitual abortion	15	3.4
Nephritic toxemia	13	2.9
Heart disease	10	2.3
Pyelitis	6	1.4
Total	272	

In the 102 labors which were related to two or more probable causes of prematurity, habitual abortion and eclamptogenic toxemia were found grouped together in 15 instances. Habitual abortion was recognized when the patient had previously aborted twice. Multiple pregnancy and eclamptogenic toxemia were in combination 11 times. Premature detachment of the placenta and syphilis were found in relation to eclamptogenic toxemia in 7 and 6 cases, respectively. One is impressed with the frequency of combined causes of prematurity and with the importance of eclamptogenic toxemia. In addition to the 108 labors in which it was the single pathology involved, toxemia was present in 43 instances where combined etiology was a factor.

Sixty labors were related to single miscellaneous causes of prematurity. The chief condition in this group were those operative procedures which were done because of maternal and fetal distress alone without apparent underlying obstetric pathology at the time. The operations included forceps delivery, bag induction of labor, and version with extraction.

Of the 819 premature infants, 216 died. There were 114 infants which were born alive yet died in two weeks, and 102 were stillborn for a gross mortality of 26.3 per cent. The 819 premature infants were analyzed in weight groups. Sixty were found to weigh between 400 and 1,000 gm. Seventy-one infants weighed between 1,000 and 1,500 gm., while 170 premature infants ranged from 1,500

to 2,000 gm. The largest group from 2,000 to 2,500 gm. totaled 518 infants. Of the 400 to 1,000 gm. group only 4 premature infants survived a two weeks' postnatal period. Many of these infants were nonviable premature infants. That is, they fell between the figures twenty-two to twenty-eight weeks in gestation and 28 to 35 cm. in length. In the 1,000 to 1,500 gm. group 13 lived. There was a marked drop in mortality when the infants weighed from 1,500 to 2,000 gm. There were 114 premature infants who survived. The best results were secured in the 2,000 to 2,500 gm. group where 472 lived (Table II).

TABLE II. ANALYSIS OF MORTALITY IN EACH WEIGHT GROUP
(Total Premature Infants 819)

WEIGHT GROUP	NO.	PER CENT MORTALITY
400-1,000 gm. (60)		93.3
Born alive and survived	4	
Born alive and died	36	
Stillbirths	20	
1,000-1,500 gm. (71)		81.7
Born alive and survived	13	
Born alive and died	35	
Stillbirths	23	
1,500-2,000 gm. (170)		32.9
Born alive and survived	114	
Born alive and died	24	
Stillbirths	32	
2,000-2,500 gm. (518)		9.1
Born alive and survived	472	
Born alive and died	19	
Stillbirths	27	
Gross mortality 26.3 per cent		

The highest infant mortality was found in relation to syphilis. In 36 premature births there were 18 deaths. Six of these infants weighed from 400 to 1,000 gm. Of infants born of mothers having a history of habitual abortion, there were 6 deaths in 15 births. Three deaths occurred in the group weighing from 400 to 1,000 gm. Of 13 infants delivered from nephritic patients, there were 5 deaths. Three of these fatalities came in the 1,500 to 2,000 gm. group. In 11 births, necessitating operative deliveries because of fetal or maternal distress not related to probable major causes of prematurity, there were 4 deaths. One death occurred in each of the 4 weight groups. Premature detachment of the placenta was found associated with 13 deaths and 38 births. There were 3 deaths each in the 1,000 to 1,500 gm. and 2,000 to 2,500 gm. weight groups. Eclampsogenic toxemia was related to 25 deaths in 108 births. In the 1,000 to 1,500 gm. and 2,000 to 2,500 gm. weight group, there were 8 deaths each. Placenta previa had 3 deaths in 14 births. Two occurred in the group weighing from 1,500 to 2,000 gm. The conclusion may be drawn that the probable causes of prematurity in our series were concurrently leading obstetric factors in premature infant death.

The association of abnormal presentations and positions with prematurity and death revealed a mortality of 36.8 per cent.

Breech presentation was present in 92 instances for an incidence of 11.2 per cent or approximately four times its normal incidence. Since breech presentation is relatively common during the last trimester of pregnancy, an increased occurrence would be expected with prematurity. There were 40 deaths related to breech delivery for a mortality of 43.4 per cent. The danger of breech delivery in the premature infant is not generally appreciated. In this study it was approximately twice that of those infants presenting by the vertex. Persistent occiput posterior was present in 41 cases. There were 8 deaths. There were 7 births with a face presenting and four with a shoulder and hand.

Operative procedures were used to effect delivery of the premature infant in 94 instances. With the exception of 11 cases previously mentioned those opera

tions were done because of probable obstetric causes of prematurity also discussed above. There were 31 deaths for a mortality of 32.9 per cent.

In 37 cesarean sections 8 fetal deaths occurred. The use of forceps on 14 occasions was related to 3 deaths, while version with extraction was associated with 4 deaths in 11 births. Eight deaths resulted from 21 attempts at bag induction of labor. The high mortality attending operative manipulations to deliver a premature infant should cause the operator to be more cautious (Table III).

TABLE III. ABNORMAL PRESENTATIONS AND POSITIONS ASSOCIATED WITH MORTALITY OF PREMATURE INFANTS

	NO.	DEATHS
Breech	92	40
Occiput posterior	41	8
Face	7	2
Shoulder and hand	4	3
Total	144	53
Group mortality 36.8 per cent		

Although the mortality of the premature infant as a whole in this study was 26.3 per cent, those infants weighing 1,500 gm. or over had a comparatively low mortality of 14.1 per cent. This low figure may be attributed partly to the fact that no barbiturates are used as analgesia in our clinic. One-fourth grain of morphine sulphate is given to the patient for rest if delivery is not expected within three hours. This is repeated when necessary. At the time of delivery, drop ether is administered as the head passes over the perineum. A left lateral episiotomy is used following thorough infiltration of the perineum with 1 per cent novocaine.

Prematurity associated with maternal age groups revealed the greatest number of premature labors in women between the ages of 20 and 25 years. There were 262 or about one-third of the total. Next in significance was the age group from 15 to 20 years, which reached 164 labors. In the period from 25 to 30 years 156 premature labors occurred. There was a gradual decline thereafter to reach a low of one premature labor in the age group of 45 to 50 years. Six labors occurred in patients from 10 to 15 years, and of these five were in colored girls.

Possible seasonal influence upon premature labor was analyzed. It was found that the greatest number of labors appeared in May, next in prominence was July and August and then December and January. Activities about the house and garden in spring were thought to influence the high incidence of premature labors in May. Increased summer temperatures possibly encouraged prematurity in July and August, while the exciting holiday season of December and January may have played an important role at that period. Recourse to the calendar as an explanation of an undetermined etiology might be of value.

Management of prematurity from an obstetric standpoint should begin with prophylactic measures. Since eclamptogenic toxemia, syphilis, premature separation of the placenta, habitual abortion, and multiple pregnancy play the most important roles as probable causes of prematurity, therapy should be directed toward control of those conditions.

Eclamptogenic toxemia which accounted for 25 per cent of the single probable causes of prematurity in our series offers a problem. Early recognition in prenatal examinations and the institution of bed rest, milk diet, and one ounce of magnesium sulphate daily will go far in keeping this condition under control. Many premature labors occurred, however, with the management of toxemia in progress. Early diagnosis of the toxemia type of patient followed by measures for its control would be a direct way of combating prematurity arising from this source.

Colvin and Bartholomew¹ have drawn our attention to the increased incidence of hypothyroidism early in pregnancy of those patients who have a tendency toward eclamptogenic toxemia. With this hypothyroidism there is a corresponding hypercholesteremia. If routine basal metabolic rates and cholesterol de-

terminations were made on all pregnant women at or about the fourth month, it might be possible to reduce the incidence of toxemia by the administration of Lugol's solution to those patients having a hypothyroidism or hypercholesteremia.

Syphilis has long been recognized as a prominent cause of prematurity. The early and adequate onset of antisyphilitic therapy would reduce this factor to a minimum. If treatment is begun before the fifth month of pregnancy, prematurity rarely occurs.

Multiple pregnancy as an important cause of prematurity stimulates early contractions of the uterus. This may be due to increased intrauterine tension or to the presence of one or more abnormal fetal positions or because of premature rupture of membranes. Premature detachment of a normally implanted or a low lying placenta will also encourage uterine contractions. These contractions stimulate further detachment and premature labor ensues. Placenta previa may be a cause of prematurity by the same reasoning applied to premature separation of the placenta. In fact, it may be extremely difficult to distinguish clinically between a low lying placental detachment and a marginal placenta previa. In the management of those conditions associated with premature uterine contractions, some form of therapy to allay uterine irritability would be in form.

TABLE IV. OPERATIVE PROCEDURES ASSOCIATED WITH MORTALITY OF PREMATURE INFANTS

	NO.	DEATHS
Cesarean section	37	8
Bag induction	21	8
Forceps	14	3
Version and extraction	11	4
Vaginal hysterotomy	3	3
Artificial rupture of membranes	4	1
Dührssen's incisions	2	2
Craniotomy	1	1
Cervical polypectomy	1	1
Total	94	31
Group mortality 32.9 per cent		

In 1936 Falls² drew attention to the advantage of using progestin to control uterine contractions in the treatment of threatened and habitual abortion. Since then because of the expense of the drug, he has adopted the use of an aqueous solution of corpus luteum extract as a means to control those conditions. Continuing his investigations, Falls has advanced the influence of corpus luteum therapy to include placenta previa, premature detachment of the placenta, premature rupture of membranes, and premature labor proper. The results which he has attained are most encouraging.³

For the patient who habitually aborts, one rabbit unit is used twice weekly early in pregnancy before the onset of symptoms. If threatened abortion occurs, one rabbit unit is used twice daily. The latter dose applies also to premature rupture of membranes, premature labor, premature separation of the placenta and placenta previa. Dosage is reduced relative to the response secured.

Management of the premature infant to reduce the operative mortality rate offers many difficulties. The younger the premature infant the less are its chances for living. In our series those infants weighing under 1,500 gm. had a mortality of 87.0 per cent. Early episiotomy and low forceps when the head is on the perineum may be used to reduce the length of the second stage. However, unindicated and unintelligent use of operative procedures may predispose the premature infant to extensive cerebral damage with possible death or insanity.⁴ This is of particular significance in the management of the premature breech. Attempts at breaking up an extended breech should be few. Efforts to depress the aftercoming head into the pelvis are to be criticized. Extreme gentleness is absolutely necessary.

Following birth, active therapy should continue during the immediate postnatal period under the supervision of an obstetrician in consultation with a pediatrician. The obstetrician should be responsible by reason of his presence at the delivery and because of his training to interpret possible obstetric causes of prematurity.

The premature infant may be overtreated as well as undertreated. Adequate heat and oxygen and frequent small feedings of mother's breast milk diluted with water are of major importance. Most premature infants take feedings through the medicine dropper well. The use of gavage is valuable. The gavage form of feeding, however, in the very young premature infant carries a great deal of shock from trauma and may defeat its purpose. To combat dehydration and to meet the infant's water requirements subcutaneous fluids are invaluable. Two ounces of 5 per cent dextrose and saline solution may be used twice daily.

In our clinic, whole blood is used in the jaundiced infant and in those infants where cerebral hemorrhage is present or suspected. Early attention to gastrointestinal upsets, upper respiratory symptoms and to cutaneous disturbances will go far in aborting a fatal diarrhea, a pneumonia, or an impetigo.

DISCUSSION

Comparable premature studies have been infrequent. Various authors have dealt with the subject of etiology, mortality, and treatment of prematurity from different angles. Clifford⁵ in 1934, Breese⁶ in 1938, Waddell⁷ in 1937, Ingram⁸ in 1937, Dunham⁹ in 1936, Hirst¹⁰ in 1939 and Swanson¹¹ in 1936 made valuable additions. Our study of the premature infant was conducted primarily from the viewpoint of the obstetrician.

Of the 765 premature labors a probable cause of prematurity could be accounted for in only 434 instances. This deficiency should encourage a concentrated attempt to determine the cause of premature delivery in all instances. Of the 216 premature deaths, 143 were associated with probable causes of prematurity. Autopsy reports were misleading. There were cases of atelectasis, slight cerebral hemorrhage, or minor lacerations of the tentorium which did not explain the cause of death. Many reports were returned with negative findings.

As a corollary to every obstetric service there should be, therefore, a committee upon whom rests the obligation of determining the cause of premature labor and birth. Coincident with this objective each premature death should have a careful investigation. This should include an autopsy study done by one skilled in the interpretation of premature infant pathology. By combining these goals successfully, the etiology and management of prematurity will be simplified and premature death will be explained upon a more rational basis.

SUMMARY

1. Of 10,797 labors with subsequent births at the Research and Educational Hospitals of the University of Illinois, 765 labors were premature. There were 52 multiple pregnancies which produced a total of 819 premature infants.

2. The probable causes of prematurity were chiefly eclamptogenic toxemia, premature detachment of the placenta, syphilis, multiple pregnancy, habitual abortion, placenta previa, nephritic toxemia, heart disease, and pyelitis.

3. There were 216 premature deaths. Probable causes of prematurity were present with premature death in 143 instances.

4. The gross infant mortality was 26.3 per cent. Infants under 1,500 gm. had an 87.0 per cent mortality, while those 1,500 gm. and over had a mortality of 14.1 per cent.

5. A thorough understanding of obstetric complications is of prime importance to manage adequately premature labor. An aqueous solution of corpus luteum extract to control premature uterine contractions is an important adjunct in the management of prematurity.

6. Skilled autopsy examination by one familiar with premature infant pathology is necessary to determine the cause of death.

REFERENCES

- (1) *Colvin, E. D., and Bartholomew, R. A.*: AM. J. OBST. & GYNEC. 37: 584, 1939. (2) *Falls, F. H.*: J. A. M. A. 106: 271, 1936. (3) *Falls, F. H.*: Unpublished Data. (4) *Mauzey, A. J.*: Illinois M. J. 74: 156, 1938. (5) *Clifford, Steward, Jr.*: J. Pediat. 5: 2, 1934. (6) *Breese, B. B., Jr.*: Ibid. 12: 648, 1938. (7) *Waddell, W. W., Purcell, V. W., and Wray, W. S.*: South. M. J. 30: 535, 1937. (8) *Ingram, C. H., Jr.*: AM. J. OBST. & GYNEC. 33: 80, 1937. (9) *Dunham, E. C., and McAllenney, P. F., Jr.*: J. Pediat. 9: 717, 1936. (10) *Hirst, J. C.*: AM. J. OBST. & GYNEC. 37: 634, 1939. (11) *Swanson, W. W., Lennarson, V. E., and Adair, F. L., Jr.*: J. Pediat. 9: 11, 1936.

1819 WEST POLK STREET

A STUDY OF RESULTS IN 332 CONSECUTIVE CASES OF PLACENTA PREVIA

ISADORE A. SIEGEL, A.B., M.D., BALTIMORE, MD.

(From the Department of Obstetrics, University of Maryland Medical School.)

THE following constitutes an analysis of 332 cases of placenta previa treated at the University Hospital from 1920 to 1938, inclusive, and at the Baltimore City Hospital from 1935 to 1938, inclusive. Since both hospitals employ the same method of treating placenta previa, and since both obstetric departments are headed by the same chief of service, together with a similarly trained attending and house staff, it is logical that these cases be grouped together.

AGE AND RACE

In the age group up to 29 years, there were 198 cases; from 30 to 39 years there were 113 cases; and from 40 years on, there were only 21 cases. This condition occurred in 214 white and in 117 negro patients. We have noted this preponderance of patients in a previous report but are unable to offer any explanation in view of the fact that we have a greater negro clinic population.

PARITY AND DURATION OF PREGNANCY

Placenta previa was found to occur in 71 (21.4 per cent) primigravidas and in 261 (68.6 per cent) multigravidas. Sixty-eight per cent of the cases occurred between the thirty-fourth week of gestation and term, thus indicating a high percentage of viable babies.

TYPES OF PLACENTA PREVIA AND METHOD OF DELIVERY

In 324 cases the type of placenta previa was noted. The marginal type occurred in 158 cases, the partial in 83 cases, and the central in 83 cases. Vaginal deliveries were employed in 74 (46.8 per cent) marginal, 26 (31.8 per cent) partial, and 17 (20.5 per cent) central placenta previa. Cesarean section was the method of delivery in 85 (53.2 per cent) marginal, 57 (68.2 per cent) partial, and 66 (79.5 per cent) central placenta previa. The total number of vaginal deliveries were 122 as compared to 209 cesarean sections.

CESAREAN SECTION AND PARITY

In the 209 cesarean sections performed, 28.8 per cent were in primigravidas and 71.8 per cent were in multigravidas. In the primigravidas delivered by cesarean section, 53.3 per cent were of the marginal type; 28.3 per cent, partial; and 18.4 per cent central. In the multiparas, 34.4 per cent were of the marginal type; 29.0 per cent, partial; and 36.6 per cent central placenta previa.

CONDITION OF THE CERVIX

In 272 cases the condition of the cervix was noted. In the vaginal delivery group, the cervix was closed in only 5 cases; the cervix was dilated between 1 and 2 cm. in 18 cases; between 3 and 4 cm. in 30 cases; and between 5 cm. and full dilatation in 38 cases. In the cesarean group, the cervix was closed in 98 cases; was dilated from 1 to 5 cm. in 83 cases; and in no case was the cervix dilated over 5 cm.

BLOOD TRANSFUSION

Since 1927 we have been employing blood transfusion with greater frequency. Thus in 195 cesarean deliveries blood was given in 27.7 per cent of the cases, while in 72 vaginal deliveries it was used in 17.57 per cent of the cases. Blood is made available for every case and is given whenever needed.

MATERNAL MORTALITY

In Tables I and II are tabulated the maternal mortality according to the method of delivery and the cause of death. It is important to note that the principal cause of death in the vaginal group is hemorrhage and in the section group it is infection. The total gross mortality was 3.62 per cent; 6.6 per cent for the vaginal deliveries, and 1.9 per cent for the cesarean section group.

TABLE I. METHOD OF DELIVERY AND MATERNAL MORTALITY

METHOD OF DELIVERY	NUMBER	MATERNAL DEATHS
Total deliveries	331	12 (3.62%)
Dilatation of cervix, internal podalic version and breech extraction	55	7
Amniotomy and spontaneous	15	0
Amniotomy and Willett clamp	4	0
Forceps	9	1
Breech extraction	8	0
Podalic version	1	0
Spontaneous	30	0
Total vaginal deliveries	122	8 (6.6%)
Classical	172	3
Low cervical	36	1
Porro	1	0
Total cesarean sections	209	4 (1.9%)

MATERNAL MORBIDITY

The maternal morbidity is three times as great in the abdominal deliveries as compared with the vaginal deliveries, 63 and 22 per cent, respectively. How-

TABLE II. CAUSES OF MATERNAL DEATHS IN 332 CASES OF PLACENTA PREVIA

VAGINAL DELIVERIES (122)		MATERNAL DEATHS	
Causes of Deaths:			
	Ruptured uterus		1
	Hemorrhage and shock		6
	Hemorrhage—not delivered		(1)
	Septicemia and peritonitis		1
Total number			8
Percentage			6.6%
CESAREAN DELIVERIES (209)		MATERNAL DEATHS	
Causes of Deaths:			
	Hemorrhage and shock		1
	Peritonitis		1
	Generalized peritonitis and paralytic ileus		1
	Hemorrhage and bronchopneumonia		1
Total number			4
Percentage			1.91%

ever, in the great number of cases the condition was very mild, just falling within the morbidity standard.

FETAL MORTALITY

The fetal mortality was 60 (48.8 per cent) and 58 (27.8 per cent) in the vaginal and section cases, respectively. While it is obvious that the fetal mortality is reduced in the section deliveries, it is more important to know what percentage of viable babies are saved in the two groups and in each type of previa. In Table III we give these figures.

TABLE III. FETAL MORTALITY. SURVIVAL OF VIABLE* BABIES AFTER DELIVERY BY VAGINA VERSUS CESAREAN SECTION

	DELIVERY BY VAGINA			DELIVERY BY CESAREAN SECTION		
	MAR-GINAL	PARTIAL	CENTRAL	MAR-GINAL	PARTIAL	CENTRAL
No. of deliveries	75	25	17	86	57	66
No. of babies	75	25	17	86	57	66
Nonviable babies	8	2	2	0	0	3
Viable* babies	67	23	15	86	57	63
Stillbirths	19	11	7	2	1	14
Neonatal deaths	8	4	2	14	10	16
Survived	40	8	6	70	46	36
Percentage of survived viable babies	59.7	34.8	40.0	81.4	80.7	57.1
Percentage of survival all types by vaginal route: 51.42 per cent						
Percentage of survival all types by cesarean route: 73.8 per cent						

*Babies weighing over 1,500 gm. and/or over twenty-eight weeks' duration.

FETAL ABNORMALITIES

We were unable to find any record of fetal abnormalities in the vaginal deliveries, but there were 5 cases in the section series. The relationship of monstrosities and congenital anomalies to placenta previa is of interest. Murphy believes that there is no greater incidence of this finding in placenta previa than over the general incidence in all cases, while Greenhill in a very exhaustive study of the literature finds that there seems to be a relationship between the two conditions.

DISCUSSION

From this study we are impressed with the importance of an early diagnosis of placenta previa employing every safe method of diagnosis, bearing in mind the need to prevent hemorrhage, to conserve and replace blood.

In the last few years we have carried out the following routine in the handling of all cases of suspected placenta previa. Every patient who has painless bleeding is immediately hospitalized. Her blood is promptly matched, grouped, and a donor secured. If a compatible donor is not available, or if the patient is bleeding seriously, we immediately secure blood from our "Blood Bank." If time permits and the patient is in good condition, a soft tissue technique x-ray is taken to visualize the placenta. If a vaginal examination is necessary to make the diagnosis as to type of previa and condition of the cervix, the operating room is set up; the operating team is ready and prepared to immediately perform a cesarean section; and all materials necessary for a vaginal delivery are on hand. Then and only then is a vaginal examination done.

The method of delivery has a definite relationship to maternal mortality. In every case the method of delivery should be individualized, depending upon the type of placenta previa, the amount of hemorrhage, the condition of the cervix, as well as the question of vaginal infection. Nevertheless, manual dilatation of the cervix with internal podalic version is to be condemned. If vaginal delivery is to be done, the most important thing to bear in mind is to control hemorrhage and then only to complete the delivery after the cervix normally becomes fully dilated. Thus rupture of the membranes with or without the use of the Willett clamp has given satisfactory results in selected cases in controlling hemorrhage, while the cervix is dilating. The same is true in bipolar version where the buttocks are used as a tamponade until the patient is ready for delivery. We almost never employ in our clinic the hydrostatic bag, for it is felt that it is less safe both from the standpoint of infection and that of hemorrhage. In the employment of cesarean section in placenta previa, we are influenced first by the type of placenta previa and second by the condition of the cervix. Thus in central and partial placenta previa we favor cesarean section. In marginal types, if the cervix is long and undilated, we likewise will perform a section, reserving the vaginal route for the dilated cervix, especially in the multipara. This is demonstrated by the fact that in the primigravida 53.3 per cent of the sections were of the marginal type as compared with 34.3 per cent in the multigravida. We have employed the low cervical section with satisfactory results.

The maternal mortality, from the point of view of the type of delivery, favors the abdominal section. This is well demonstrated by the fact that over a period of eighteen years, with more careful selection of cases for vaginal delivery, we have been unable to reduce our maternal mortality, while in the same period of time with the employment of the cesarean section, we have definitely and gratifyingly reduced it.

Findley, after an analysis of 47,828 cases of placenta previa collected from world-wide literature states, "The incidence of cesarean section has increased from 6.07 per cent to 15.29 per cent during the past fifteen years while the maternal mortality rate has been more than halved and falls way below the group delivered from below." The importance of liberal blood transfusions and the great help of having blood available at all times in the form of a "Blood Bank" is life saving in many instances.

From the point of view of the baby, it is well-recognized that the best chances for life of the baby is by abdominal delivery. In this study we are struck by two considerations: first, the greatest number of cases is beyond the thirty-second week of pregnancy; and second, the survival of viable babies is greatly increased by cesarean section in all types of placenta previa. For these reasons, without increasing the risk of the mother by cesarean section in properly selected cases, we should give the baby its best chance for survival.

SUMMARY AND CONCLUSIONS

1. The results of 332 consecutive cases of placenta previa are presented.
2. The more frequent and liberal use of blood transfusions is paramount in reducing maternal mortality and morbidity.
3. The method of delivery must be determined for each individual case, depending upon the type of placenta previa and the condition of the cervix.
4. Accouchement forcé, internal version and breech extraction are condemned in the treatment of this condition.
5. The rupture of membranes with or without the use of the Willett clamp will give favorable results in the properly selected cases.
6. The employment of cesarean section definitely reduces the maternal and fetal mortality in the central and partial types of placenta previa and in certain selected cases of marginal placenta previa.
7. The maternal mortality in this series is 6.6 per cent in vaginal deliveries and 1.9 per cent in cesarean section.
8. Deaths in viable babies are greatly reduced by the employment of cesarean section.

REFERENCES

- Douglass, L. H., and Siegel, I. A.: *AM. J. OBST. & GYNEC.* 15: 671, 1928.
Findley, David: *Ibid.* 36: 267, 1938. Greenhill, J. P.: *Ibid.* 37: 624, 1939.
Murphy, D. P.: *Ibid.* 35: 653, 1938. Siegel, I. A.: *Ibid.* 22: 110, 1931. *Idem*: *Ibid.* 27: 889, 1934.

A STUDY OF 111 CYSTOGRAMS FOR DIAGNOSIS OF PLACENTA PREVIA*

MILTON A. CARVALHO, A.B., M.D., BINGHAMTON, N. Y.
(From the Margaret Hague Maternity Hospital, Jersey City, N. J.)

THE purpose of this paper is to present a comprehensive study of the use of the cystogram in the diagnosis of placenta previa and to point out certain failures of the method. The work was first undertaken about May, 1937. A preliminary report covering 19 cases was prepared by me in collaboration with Dr. John A. McGeary and read before the Section on Obstetrics, at the New York Academy of Medicine, Nov. 23, 1937. The present report includes those cases and others collected during the intervening period up to October, 1938. During this time a total of 111 cystograms were done on 105 patients in the third trimester of pregnancy.

Until 1934 various methods⁷ were used in conjunction with the x-ray for the diagnosis of placenta previa. Since all of these methods involved the injection of foreign materials directly or indirectly into the uterine cavity, they entailed the dangers of intrauterine infection, premature rupture of the membranes, premature induction of labor, fetal death in utero, intrauterine hemorrhage, or perforation of maternal (occasionally fetal) viscera. Snow and Powell⁸ in 1934 wrote that with careful study one could locate the placental site in the ordinary anteroposterior or lateral films of the abdomen. Other authors pointed out that calcifications in the mature placenta could be visualized in the usual films of the abdomen.

In the same year Ude, Weum, and Urner¹² suggested the use of the cystogram, and in 1935 Ude and Urner^{9, 10} reported its use in 35 cases of third trimester bleeding.

In the present series the technique of Ude and Urner has been followed. There were 105 patients upon whom 111 cystograms were done. The discrepancy is accounted for by repetition on those few cases which were admitted to the hospital more than once during the same pregnancy, or who were kept under observation for longer than usual. For the purposes of this paper the cases are divided into three groups:

1. Patients proved not to have had placenta previa at the time of parturition.
2. Patients in whom placenta previa was demonstrated at the time of delivery.
3. Patients with presentations other than vertex.

RESULTS

There were 78 patients in whom placenta previa was not found when they delivered. Of these, 17 were controls without a history of bleeding, and the remainder were patients who gave a history of third trimester bleeding. There were 83 cystograms done on these 78 patients. In none of the 17 controls was an x-ray diagnosis of placenta previa made, and in none of them was it dem-

*Read at a meeting of the Broome County Medical Society, Oct. 10, 1939.

onstrated at delivery. However, in the remaining 61 patients, of a total of 66 cystograms done, 10 showed x-ray evidence pointing toward placenta previa which was not substantiated at the time of parturition.

Every patient in this series was examined vaginally at the time of delivery to determine the site of implantation of the placenta. Nine patients came to cesarean section for other causes; 14 patients showed evidence of a partial premature separation of the placenta at delivery. In none of the latter was there any abnormal space between the head and the bladder which might have been caused by blood clots as mentioned by Ude and Urner.^{9, 10}



Fig. 1.—Case 13. A. R., multipara, with painless vaginal bleeding at seven and one-half months. Cystogram shows greatest distance between head and bladder 0.4 cm. Vaginal examination showed edge of placenta to right and posterior, with 2 fingers' dilatation of the cervix.

There were 8 patients in whom a false diagnosis of placenta previa was offered on the evidence of the cystogram. Seven of these patients were delivered vaginally and showed no placenta previa. One of these 7 demonstrated a partial premature separation of the placenta, which was situated high in the fundus. There were no clots in front of the head which might have caused the increased vesicocephalic space. The eighth patient was delivered by cesarean because of cephalopelvic disproportion; no previa was found.

It seems rather obvious from the foregoing cases that false positive reports may occur. The explanation is difficult to deduce. All of these cases had been done before publication of a paper by Ude, Urner, and Robbins¹¹ came to our attention. They urged administration of low colonic flushes before x-ray, feeling that distention of the rectum with feces and gas has frequently caused upward displacement of the head,

giving rise to a false positive interpretation of the film. Subsequent review of the cystograms in the above cases showed gas and feces present in all. This may be the explanation in these cases, but rectal contents are visible in most of the negative plates also. Obviously the upward displacement of the head depends on the quantity of the rectal content.



Fig. 2.—Case 15. M. R., 39 years old, primigravida, with vaginal spotting three or four days, at 8 months' gestation. Cystogram shows space between vertex and bladder of 4.4 cm. in midline and 4.5 cm. on right, 3.5 cm. on left. Cesarean section two weeks later, placenta implanted posteriorly except for anterior one-third which covered cervix and lower segment on anterior wall to level of vesicouterine peritoneal reflection.

In the eighth patient mentioned above, at operation the bladder was found situated high on the lower uterine segment, adherent to the upper portion of a previous low vertical incision. This circumstance may well be analogous to one mentioned by Ude, Urner, and Robbins¹¹ in which there was a nonoperative upward displacement of the bladder, giving rise to a false positive cystogram.

There were 19 patients in this series in whom placenta previa was found. Nineteen cystograms were done, placenta previa was correctly prognosticated in 13,

68.42 per cent. It was incorrectly ruled out in 6 cases, or 31.58 per cent. Four patients came to cesarean section for placenta previa. The remainder were delivered vaginally and the diagnosis so checked. In one case there was a prolapsed arm in front of the head which caused a characteristic indentation in the placental shadow over the bladder.

In all six cases where placenta previa was incorrectly ruled out by the cystogram, the placenta was found implanted on the posterior wall of the lower segment, with varying portions of the placenta overhanging the cervical os (Fig. 1). Four patients had a partial placenta previa, two had marginal previa. In one patient (F. L.), Cystogram 7972 showed the head impinging on the bladder, while vaginal examination demonstrated the cervix $2\frac{1}{2}$ fingers dilated with the placenta implanted directly on the posterior wall, covering about three-fourths of the os.

By contrast the following case of posterior implantation is detailed: M. R., a 39-year-old, white, para 0, gravida i, admitted because of vaginal spotting for three or four days. Uterus the size of an eight months' gestation, fetus small, head high. Cystogram 8946 showed a space between the vertex and bladder of 4.4 cm. in the midline and on the right, and 3.0 cm. on the left (Fig. 2). A probable diagnosis of placenta previa centralis was offered. Two weeks later with onset of further bleeding, cesarean section was done, and the placenta was found implanted on the posterior wall, except for the anterior one-third which covered the cervix and the lower segment on the anterior wall to the level of the vesicouterine peritoneal reflection.

It is interesting to note that in all of the cases where placenta previa was incorrectly ruled out by the cystogram the placenta was found implanted on the posterior wall, with only the margin, or one or two cotyledons overhanging the os. Furthermore it is logical that such an implantation should not displace the head upward sufficiently to give the characteristic cystogram. The placenta must be between the head and bladder in order to show such a relationship. Unless enough of a posteriorly implanted placenta extends over the os and upward on the anterior uterine wall sufficiently to widen the space between the head and the bladder, the interpretation will be negative. This is illustrated by the six cases mentioned above as contrasted with the case of M. R. where such a situation existed.

Until November, 1937, when a preliminary report of this work was read, the literature was void of any mention of the posteriorly implanted placenta previa, perhaps because such an implantation was considered marginal and of little danger. In the present series the classification of marginal, partial, and central previa has been based on a theoretical full dilatation of the cervix. Thus a marginal in relation to a closed cervix or with one fingerbreadth dilatation becomes a partial previa in relation to a fully dilated cervix. It has been our experience that the posteriorly implanted previa has all the dangerous potentialities of the anterior or lateral implantation. In the preliminary report mentioned above there was included one case of posterior placenta previa, and at that time we pointed out the impossibility of cystogram diagnosis in such circumstances. Since that time (until October, 1938), only one report, that of Jablonski and Meisels,⁴ mentions that a posteriorly situated placenta previa may be overlooked. From a personal communication with Dr. Alfred C. Beck in May, 1938, I learned that in two of Beck's cases where the cystogram had failed to diagnose placenta previa, it had been found implanted posteriorly.

There were 9 cystograms taken on 8 patients with the breech presenting. In one case the first cystogram showed the breech 3.5 cm. above the bladder; the second cystogram twelve days later showed the breech sitting on the bladder shadow. Of the 9 cystograms, 2 were useless because of poor delineation, 22.22 per cent; placenta previa was incorrectly diagnosed in three, 33.33 per cent; incorrectly ruled out in two, 22.22 per cent; and correctly ruled out in two, 22.22 per cent. With such a marked variability, even though only a few breeches are considered, the cystogram seems of questionable value here.

In the whole series of 111 cystograms (see Tables I and II), the diagnosis by x-ray was correct in 88 instances (79.28 per cent), incorrect

TABLE I

Group 1: No placenta previa at delivery	
Controls	17
Bleeding cases	61
Total cystograms	83
X-ray diagnosis correct	73 (87.95%)
X-ray diagnosis incorrect	10 (12.05%)
Group 2: Placenta previa found at delivery	
Cases	19
Cystograms	19
X-ray diagnosis correct	13 (68.42%)
X-ray diagnosis incorrect	6 (31.58%)
Group 3: Presentations other than vertex	
Cases	8
Cystograms	9
X-ray diagnosis correct	2 (22.22%)
X-ray diagnosis incorrect	5 (55.55%)
X-rays useless	2 (22.22%)

TABLE II

Summary of series	
Cases	105
Cystograms	111
Placenta previa correctly diagnosed	13 (11.71%)
Placenta previa correctly ruled out	75 (67.57%)
Placenta previa incorrectly diagnosed	13 (11.71%)
Placenta previa incorrectly ruled out	8 (7.21%)
Useless plates	2 (1.80%)
Total correct diagnoses	88 (79.28%)
Series with breeches eliminated	
Cases	97
Cystograms	102
Placenta previa correctly diagnosed	13 (12.75%)
Placenta previa correctly ruled out	73 (71.57%)
Placenta previa incorrectly diagnosed	10 (9.80%)
Placenta previa incorrectly ruled out	6 (5.88%)
Total correct diagnoses	86 (84.32%)

in 21 instances (18.92 per cent), and there were two useless plates (1.80 per cent). If the breeches are eliminated from the study, we have a total of 102 potentially useful cystograms; the x-ray diagnosis was correct in 86 instances (84.32 per cent), incorrect in 16 instances

(15.68 per cent). These figures may be compared with those of Beek and Light¹ who eliminated from their study the cases in which the vertex was not presenting. In their 71 cases of third trimester bleeding, diagnosis was correct in 63 (88.73 per cent), and incorrect in 8 (11.27 per cent). Whereas Beek and Light found placenta previa correctly diagnosed in 13 of 17 cases (76.47 per cent), and its absence correctly diagnosed in 50 of 54 cases (92.59 per cent); in the present series placenta previa was correctly diagnosed in 13 of 19 cases (68.42 per cent), and its absence correctly diagnosed in 73 of 83 cystograms taken on 79 cases (87.95 per cent).

DISCUSSION AND SUMMARY

The cystogram has been found useful as an aid in the diagnosis of placenta previa, but like all other laboratory tests, the findings must be weighed together with the clinical facts. It has been our practice to examine vaginally every case of third trimester bleeding on the ward service regardless of the x-ray report. In those cases where the report was negative, examination was made for corroboration and to ferret out the cause of the bleeding. In cases where x-ray offered a provisional diagnosis of placenta previa, examination was conducted in the operating room with a blood donor available. Where a positive diagnosis was offered and the patient had ceased bleeding, she was observed at bed rest in order to carry the child to a period of greater viability. If, however, bleeding recurred she was examined as above.

In cases where placenta previa is falsely postulated by the cystogram, no harm has been done. The upward displacement of the head may frequently be due to a distended rectum and sigmoid. The use of the colonic flush as advocated by Ude, Urner, and Robbins¹¹ before indirect placentography must of course depend upon the circumstances of the case. Needless to say, one is not going to give rectal treatment to a patient who is actively bleeding. Since the female rectum is almost always occupied by varying amounts of feces and gas, and since a false positive report was offered in only 9.80 per cent of 102 cystograms, we feel that the rectal flush may well be reserved for the patient who ceases bleeding. No patient should be discharged until she has been examined vaginally under aseptic precautions to determine the cause of the bleeding.

If all patients are subjected to such examination the posterior implantations, where a false negative report has been given, will be discovered and catastrophe at home avoided. An attempt was made by us to utilize the lateral plate to diagnose the posterior implantations. This was a failure in general although a small number were postulated. A review of a considerable number of laterals taken during routine pelvic stereoroentgenography showed no constant variation in the distance of the fetal head from the promontory of the sacrum in the seventh, eighth, or ninth month of gestation. Perhaps the development of a greater familiarity with the methods of Snow and others in the delineation of the placenta by soft tissue technique will help to solve this problem.

CONCLUSIONS

1. The cystogram is useful in the diagnosis of placenta previa, but should always be correlated with the clinical findings.
2. A false positive diagnosis may be caused by upward displacement of the fetal head due to rectal distention. This can be corrected by rectal flushes in certain cases.
3. A placenta previa which is implanted on the posterior wall of the lower uterine segment with no portion thereof intervening between the fetal head and the bladder cannot be diagnosed by indirect placentography.
4. No patient with a history of third trimester bleeding should be discharged without a careful vaginal examination under proper precautions.

The author gratefully acknowledges the many helpful suggestions and constructive criticisms freely given by the staff of the Margaret Hague Maternity Hospital, and in particular wishes to thank the following for their whole-hearted cooperation and help: Drs. S. A. Cosgrove, J. F. Norton, E. J. Waters, H. J. Perlberg, and J. A. McGeary.

REFERENCES

- (1) Beck, A. C., and Light, F. P.: *AM. J. OBST. & GYNEC.* 35: 1028, 1938.
- (2) Hall, S. C., Currin, F. W., and Lynch, J. F.: *Ibid.* 33: 625, 1937. (3) Hundley, J. M., Walton, H. J., et al.: *Ibid.* 30: 625, 1935. (4) Jablonski, K., and Meisels, E.: *Zentralbl. f. Gynäk.* 62: 532, 1938. (5) McDowell, J. F.: *AM. J. OBST. & GYNEC.* 33: 436, 1937. (6) McIver, Julius: *Tex. State J. Med.* 32: 471, 1936.
- (7) Priest, Robert E.: *Minn. Med.* 20: 163, 1937. (8) Snow, William, and Powell, Chillian B.: *Am. J. Roentgenol.* 31: 37, 1934. (9) Ude, W. H., and Urner, J. A.: *Minn. Med.* 18: 9, 1935. (10) *Idem*: *AM. J. OBST. & GYNEC.* 29: 667, 1935. (11) Ude, W. H., Urner, J. A., and Robbins, O. F.: *Am. J. Roentgenol.* 40: 37, 1938.
- (12) Ude, W. H., Weum, T. W., and Urner, J. A.: *Am. J. Roentgenol.* 31: 230, 1934. (13) Wells, W. W.: *J. Oklahoma Med. Assn.* 30: 285, 1937. (14) Williams, E. R.: *Brit. J. Radiol.* 11: 202, 1938.

37 FRONT STREET

GÄRTNER'S DUCT LESIONS OF THE CERVIX

SAMUEL A. WOLFE, M.D., F.A.C.S., BROOKLYN, N. Y.

(From the Department of Gynecology and Obstetrics, Long Island College of Medicine)

GÄRTNER'S duct represents the persisting distal segment of the Wolffian or mesonephric duct. Its presence in the adult female is a phylogenetic anomaly. The cranial end of the Wolffian duct, however, is generally retained and unites with the proximal collecting tubules of the primitive kidney to form the epoophoron. This embryonal structure is normally encountered in the mesovarium and the lateral third of the mesosalpinx. The line of demarcation between the proximal and distal segments of the mesonephric duct has been shown by Robert Meyer to lie at a point between the caudal pole of the ovary and the wall of the uterovaginal canal. This has been demonstrated in a human embryo 30 mm. in length. With formation of the uterus and vagina, Gärtner's duct proceeds inferiorly between the layers of

the broad ligament and not uncommonly enters the outer wall of the uterus. In Japanese women, J. Sakuraoka, found rests especially frequent in the corpus uteri, generally at the level of the round ligament and in the isthmus at the level of the internal os. Rests in the supravaginal cervix and portio, which are sites of predilection in the European female, were noted with less frequency. Leaving the uterus at the cervicovaginal junction, the duct further descends in the lateral wall of the vagina to reach the hymenal edge. The course of the duct, however, in both uterus and vaginal wall is extremely varied.

Persistence of Gärtner's duct *in toto* is rare. J. Sakuraoka records such a case in a 53-year-old woman. Small segments of the duct, however, are found in about 20 per cent of all adult females. The left side is apparently favored. The incidence increases after the age of seventeen, largely the result of growth of the duct which renders its recognition easier. Rests in the supravaginal cervix are most frequent, especially at the level of the internal os where the duct enters from the broad ligament and proceeds medially and inferiorly to lie close to the endocervix. Continuing into the vaginal section of the cervix, it turns laterally to reach the outer aspect of the portio where it generally terminates.

When observed microscopically, the morphology of the duct is distinctive. It presents as a simple tube which gradually widens as it proceeds inferiorly, and in the upper portion of the vaginal cervix produces an ampulla which is comparable to that of the vas deferens in the male. As it further descends the ampulla divides into branches which terminate in gland clusters. The branches are spiral, of small caliber, and generally proceed from the anterior and posterior aspects of the widening duct. They are concentrically arranged in relation to the inner surface of the cervix. The lumen of the main duct presents a distinctive lining of low cuboidal or flat epithelium. The cytoplasm is scant and clear. A small round or oval vesicular nucleus almost completely fills the cell body. The glands which originate by sacculation are generally round or oval and of small dimension. The lining epithelial cells are also cuboidal or low columnar with a poorly defined cell membrane. The cytoplasm is pale, and here too a round vesicular nucleus almost completely fills the cell body. The lumina not uncommonly contain secretion.

In a series of 1413 cervixes examined in the Gynecology Laboratory of the Long Island College of Medicine, between the years of 1923 and 1938, only one contained normal remnants of Gärtner's duct. The explanation for the infrequent occurrence lies in the fact that surgical transection of the cervix is performed below the level of the internal os where Gärtner's duct rests are most frequently encountered.

CASE REPORT

The solitary specimen showing Gärtner's duct was from Mrs. B. S., aged 35 years (31,722), who was admitted with complaints of vaginal discharge and backache. A lacerated pelvic floor and cystoectoceles were encountered. The cervix was large, lacerated, and markedly eroded. Operation performed Jan. 23, 1937, consisted of amputation of cervix, anterior and posterior colpoplasty, and vaginal

sterilization. The cervical cone which was radically amputated measured 25 mm. in length, 20 mm. transversely at the external os, and 20 mm. transversely at the apex. Both lips presented marked erosion of the papillary type. The endocervical mucosa was congested and its markings were prominent. The segment of muscle was fibrotic. The microscopic examination confirmed these gross observations. The posterior lip in addition showed remnants of Gärtner's duct, its radiating branches, and glands. The main canal proceeded downwards in a plane parallel to the long axis of the cervix and lay close to the endocervical mucosa (Fig. 1). Though relatively uniform it widened slightly as it continued inferiorly. Terminal branches proceeding obliquely from the main duct extended into the fibromuscular layer of the cervix to divide into gland clusters which occupied interstices between the muscle fibers. At the upper and lower extremities intraductal papillary formation was observed (Fig. 2). The lining epithelium of the main duct and its larger terminals varied from the cuboidal to

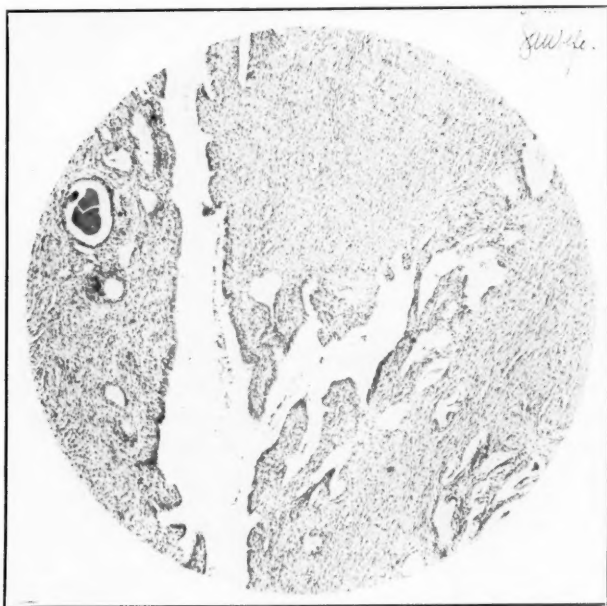


Fig. 1.— $\times 80$. Gärtner's duct is noted to the left. One of its larger branches and the terminal glands are shown well in the fibromuscular coat of the cervix. The solitary layer of low columnar or cuboidal cells is distinctive. The cytoplasm is scant and pale, and the vesicular nucleus almost completely fills the cell body.

the flat type. The cells were small and with poorly defined cell membranes. The scant pale cytoplasm was filled by a round or oval vesicular nucleus, with a fine chromatin net work. The glands about the terminals were varied. Some were round, others oval, convoluted or papillary in contour (Fig. 3). The solitary layer of lining cells was somewhat taller than in the ducts. The cell membrane was focally recognizable. The morphology otherwise was similar. Secretion occasionally encountered was homogeneous and markedly acidophilic. About the main duct was a thin layer of loose, edematous cellular stroma. The glands, however, as previously observed were scattered between normal muscle and connective tissue fibers of the cervix.

The second specimen of cervix with normal Gärtner's duct rests was obtained after hysterectomy from Mrs. L. Z., aged 44 years (No. 31,801), admitted to the Long Island College Hospital, Feb. 4, 1937, complaining of intermittent lower abdominal pain and progressive menorrhagia. An abdominal tumor, solid in type, originated from the pelvis and extended practically to the ensiform process.



Fig. 2.— $\times 80$. Gärtner's duct, branches, and terminal glands are reproduced. Note the intraluminal papillae. The solitary layer of cuboidal cells is characteristic.

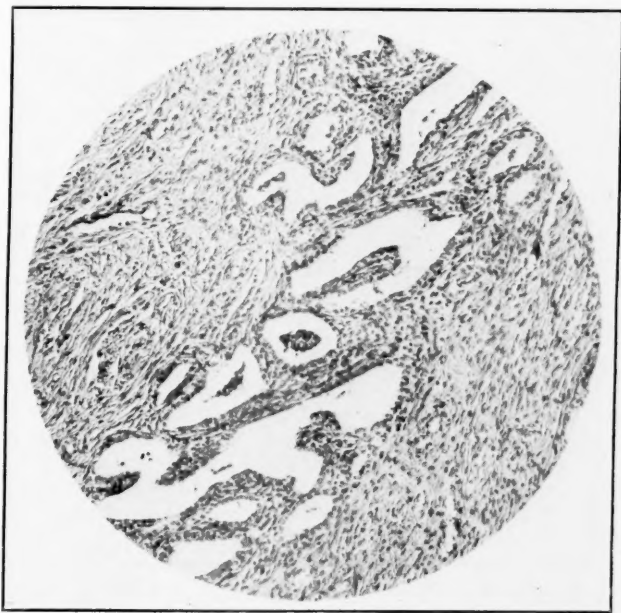


Fig. 3.— $\times 200$. Glands of Gärtner's duct origin. Round, oval, and papillary forms lie in the fibromuscular wall of the cervix. The lining cells are cuboidal or low columnar and contain faintly staining cytoplasm. The round pale nucleus almost fills the cell body.

Pelvic examination revealed a nulliparous introitus. The uterus was enlarged as outlined above and contained numerous fibroids. On Feb. 6, 1937, supracervical hysterectomy and bilateral salpingo-oophorectomy were performed. As the site of transection was close to the portio, a large segment of vaginal cervix and the entire supravaginal cervix was included. Gross and microscopic examination of the cervix revealed no special abnormalities. However, lying in the inner muscle fasciculi of the supravaginal cervix was a duct coursing parallel and close to the endocervix. It widened slightly in its descent. At its upper and lower portions, its lumen was irregular due to the formation of short papillas and the appearance of the irregular funnel-shaped incisurae. At either extremity lay collections of gland spaces, some of them encroaching upon the endocervix proper. The main duct presented a solitary layer of cuboidal cells. The cell membrane was not sharply defined. The cytoplasm was relatively scant and pale. The bulk of the cell body was filled by a round nucleus vesicular in character containing fine chromatin granules. The wide incisurae and gland spaces presented a similar lining epithelium. The glands presented a varied form. Some were round or oval, others showed papillary formation or were irregularly branched. Several contained deeply staining acidophilic secretion. The fine terminal glands which lay at some distance from the main duct were generally small in size but presented the characteristic epithelium. The stroma immediately subjacent to the main duct was comprised of cellular connective tissue but the terminal branches and glands were scattered in the fibromuscular layer.

ADENOMATOID HYPERPLASIA

Adenomatoid hyperplasia of Gärtner's duct glands has been infrequently recorded in the literature. In 1907, Robert Meyer, reporting detailed studies of normal Gärtner's duct rests in the human embryo, observed adenomatoid and papillary proliferation in the ampulla of the duct of a seven months' fetus. Rockstroh in 1935 reported two other cases of adenomatoid hyperplasia. In the first patient the lesion grossly consisted of small cysts occupying the cervix. Histologically the glands of varied size were lined by cuboidal cells. In the second case, a cervical polyp was removed and in addition biopsy of the cervix was performed. In the biopsy section, the proliferating glands of Gärtner's duct were accidentally found.

Two cases of adenomatous hyperplasia of Gärtner's duct rests have been noted in our laboratory studies.

The first, Mrs. A. N., aged 39 years (No. 24,044), was admitted to the Long Island College Hospital, Jan. 4, 1933, complaining of dysmenorrhea. Appendectomy was performed seventeen years ago without incident. A second laparotomy for supposed pelvic disorder was performed two years prior to admission. The menses which have always been regular, began at thirteen, recurred every twenty-eight days and lasted for two to three days. The patient had been married for fifteen years. The first pregnancy terminated in a spontaneous abortion at two months. The second pregnancy ten years ago was uneventful. The present illness began seven months ago and was described as pelvic pain starting with slight cramps the day prior to onset of flow, progressing in severity during the period, and persisting for four to five days after cessation of the menses. Vaginal examination revealed a parous introitus with good anterior and posterior walls.

The cervix was enlarged, firm and lacerated. The body of the uterus was slightly enlarged and contained several small fibromyomas which were irregularly distributed in the fundus. These were insensitive. The tubes and ovaries presented no apparent pathology. The posterior fornix contained two small nodules about $1\frac{1}{2}$ cm. in diameter, which impinged upon the posterior wall of the cervix just above the cervicovaginal junction. They were sensitive and pressure upon

them produced the subjective discomfort noted by the patient during menses. Operation on January 5 consisted of curettage and amputation of the cervix. The nodules in the cul-de-sac were not removed. Upon pathologic examination, the curettings showed classical changes of premenstrual endometrium. The amputated cervical cone measured 25 mm. in length, 35 mm. transversely at the portio, and 10 mm. transversely at the apex. The external os was lacerated. The squamous lining of the portio was normal. Just within the external os there were three small Nabothian cysts. The endocervix presented no other abnormalities. The muscle was fibrotic. Microscopically, the squamous lining of the portio presented hyper- and parakeratosis. The underlying connective tissue showed a slight exudate of lymphocytes and occasional plasma cells. The glands of the endocervix were hypertrophied and actively secreting. The stroma was edematous and also presented occasional lymphocytes and plasma cells. The fibromuscular wall showed advanced atrophy of the muscle fasciculi which were

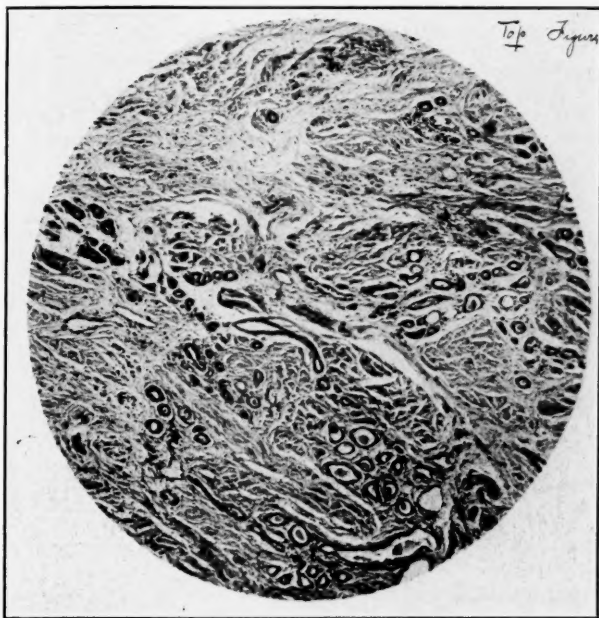


Fig. 4.— $\times 80$. Adenomatoid hyperplasia of Gartner's duct. The muscle layer of the cervix contains proliferating glands which are round, oval, or somewhat crescentic. Several contain secretion. The solitary layer of low columnar cells presents oval dark-staining nuclei. Flat and cuboidal cells, however, are encountered in some of the glands.

largely replaced by hyalinized connective tissue. At the apex of the cone about 2 to 3 mm. from the endocervix, the posterior lip contained collections of glands in its fibromuscular stratum. They were generally small, but some of moderate caliber were irregularly intermingled and suggested terminal branches of Gartner's duct (Fig. 4). The glands were round, oval, or slightly elliptical in shape and presented a solitary layer of epithelial cells. These were generally low columnar but cuboidal, and flat endothelial forms were also present. The cell membrane was poorly defined, the cytoplasm scant and pale. The oval or elongated nucleus filled the cell body and though vesicular, stained intensely, showing a dense chromatin net work. Secretion was not uncommonly encountered. The gland collections, though somewhat radially grouped about the terminals, were separated by muscle and connective tissue fibers which were edematous. The postoperative course was uneventful. Relief from comenstrual pain, however, was not obtained and accordingly two x-ray treatments were administered

in June, 1933. This was followed by amenorrhea and gradual involution of the cul-de-sac nodules, thus indicating their relation to pelvic endometriosis rather than to aberrant Gärtner's duct remnants in the supravaginal cervix. Adenomatoid hyperplasia of Gärtner's duct was only incidental. The large numbers of glands, their small size and deep-staining nuclei were all indicative of true proliferation of Gärtner's duct rests, rather than retention of incompletely involuted normal segments observed in the two previous cases.

The second case of hyperplasia was found in the cervical polyp of Mrs. L. F., aged 47 years (No. 33,815), who was admitted to the Long Island College Hospital, Feb. 13, 1937, complaining of vaginal bleeding. The previous history was uneventful. Menstruation began at fourteen, recurred regularly every twenty-eight days and continued for three to four days. The patient had been married for twenty years. There were seven pregnancies. Five terminated in normal

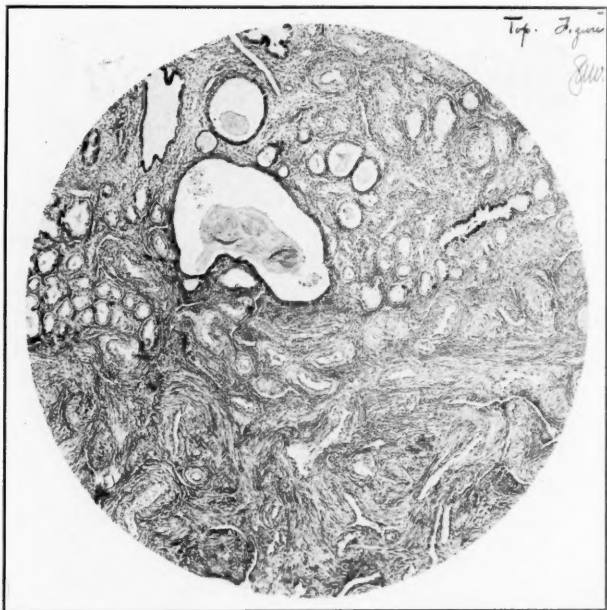


Fig. 5.— $\times 80$. Adenomatoid hyperplasia of Gärtner's duct glands in a submucous fibroid. The fibromuscular matrix of the myoma is covered by a layer of endometrium. Lying between the muscle fibers and extending into the mucosa are large numbers of small, pale, round, or oval glands, frequently containing secretion. They present a solitary layer of cuboidal or low columnar cells with pale-staining cytoplasm and a small vesicular nucleus. Note the irregular endometrial glands with tall deeply staining nuclei.

full-term deliveries, two in spontaneous uncomplicated abortions. The present illness began one year prior to admission and consisted of prolongation of the menstrual flow associated with cramplike pain in the right lower abdomen. The physical findings were essentially negative. Pelvic examination, however, revealed a lacerated pelvic floor with moderate cystocele. The cervix was irregularly lacerated, fixed in the vault and presented a polyp which was just visible in the dilated cervical canal. The uterus proper was small and posterior. The laboratory data were essentially negative. On Feb. 15, 1937, the polyp was removed. This was followed by curettage and insertion of radium. Upon pathologic examination, the curettings showed multiple endometrial polyps. The large polyp noted in the cervical canal measured 25 mm. in length, 14 mm. transversely at the tip and 4 mm. transversely at the site of transection. It was firm in consistency and upon cut section was gray white and fibrous. Microscopically,

it presented an endometrial lining which, however, was only focally encountered. At the tip it was replaced by infected granulation tissue. Where retained, the mucosa presented a lining layer of columnar epithelium, resting upon an underlying zone of edematous embryonal connective tissue. This supported occasional glands which occurred at irregular angles from the surface. They were of moderate size and generally round or oval in contour, but cystic, saccular, and irregularly branched forms, were also present. The lining cells of the glands were columnar and nonciliated. The cell membrane was poorly defined, the cell cytoplasm scant. The nucleus filling the cell body was oval or fusiform in shape and stained deeply. The bulk of the polyp, however, consisted of smooth muscle fibers concentrically arranged about large numbers of arterioles and venules. Sheaths of muscle and connective tissue cells also interdecussated at irregular angles. About the middle of the polyp but limited to only one of its surfaces, the muscle zone presented collections of proliferating glands which encroached upon the endometrial lining (Fig. 5). The individual glands though separated by muscle and connective tissue fibers were radially arranged about wider duct branches often filled with deeply staining secretion. These were lined by flat or low cuboidal epithelial cells. The gland spaces were small, round, oval, or slightly tortuous in form. The lumina were of varied dimensions and often contained acidophilic secretion. The lining cells varied from cuboidal to the low columnar type. The cell membrane could occasionally be identified. The cytoplasm was scant and stained faintly. The vesicular pale nucleus which was round or oval in form almost filled the entire cell body, but contrasted sharply with the deep-staining oval or fusiform nuclei of the endometrial glands. Histologically, therefore, the polyp was a small submucous fibroid clothed by endometrium. Gärtner's duct terminals and glands were found in the muscle zone and encroached upon the mucosa. Their relation to the submucous fibroid is difficult to estimate. Most likely pressure by proliferating tumor cells caused hyperplasia of Gärtner's duct rests, accidentally located in the zone of myomatous growth.

TUMORS OF GÄRTNER'S DUCT ORGAN

Benign tumors of this group are extremely rare. W. Rust records such a case accidentally encountered in a biopsy section from the cervix. About 0.5 cm. above the portio, the cervical muscle contained glands reminiscent of the sweat gland type. They varied from the size of a capillary lumen to cystic structures recognizable to the naked eye. Round, oval, papillary, and irregular saccular forms were present. These were lined by a solitary layer of epithelium of cuboidal form with translucent cytoplasm and a large nucleus which filled the cell body.

Malignant tumors of Gärtner's duct origin are recorded with slightly greater frequency. A case of cervical adenocarcinoma of this histogenesis was reported by Robert Meyer in 1907. G. A. Wagner also recorded a similar tumor in 1929. Rockstroh in 1935 also reported a malignant neoplasm of Gärtner's duct type. There was good response to radium.

No specimen of malignant Gärtner's duct tumor of the cervix was encountered in our laboratory. The clinical and pathologic characters of a benign papillary adenoma of Gärtner's duct origin is recorded in the case of Mrs. P. K., age 31 years (16,200), admitted to the Brooklyn Jewish Hospital, Dec. 28, 1933, complaining of pain in the right lower quadrant. The family and past personal history was essentially negative. Menstruation began at age of 15, recurred irregularly every six to eight weeks, and lasted for four to five days. The flow was associated with severe comenstrual pain which incapacitated the patient on the first day. There was little change in menstruation after her marriage in June, 1925. The first delivery in 1927 terminated in a stillbirth at term. The second confinement on June 23, 1930, was three and one-half weeks premature, and

terminated in the birth of living twin girls. Examination six weeks post partum revealed a good pelvic floor and anterior wall. The cervix was slightly lacerated. The uterus in the second degree retroversion was fairly well involuted. A pessary for displacement was refused. On Sept. 6, 1933, the patient presented herself for examination, complaining of constant pain in the right lower quadrant and discharge. The vaginal mucosa was slightly injected. The uterus was in the first degree retroversion. The right ovary was palpable. A nodule the size of a hazelnut was noted along the course of the right uterosacral ligament and was fused with the posterior aspect of the supravaginal cervix. On Oct. 20, 1933, the discharge had cleared but pain persisted. Pelvic examination revealed a definite increase in the size of the nodule at the junction of the cervix and right uterosacral ligament. A second nodule was now also palpable to the left and slightly above the node previously noted. The patient was referred to the hospital with the diagnosis of "adenomyoma of the cul-de-sac and rectovaginal septum."



Fig. 6.— $\times 80$. True adenoma of Gärtner's duct. The tumor is comprised of a matrix of hyalinized connective tissue and involuntary muscle in which are embedded large gland spaces filled by numerous broad papillas.

Upon admission the above findings were confirmed. Proctoscopic examination showed a pale, glistening rectal mucosa. The blood vessels, however, were engorged. A diagnosis of "extrarectal neoplasm" was made. On Dec. 30, 1933 a barium enema showed no obstruction, dilatation or irregularity of the bowel. The laboratory data were negative. Operation was performed Jan. 2, 1934, under gas-oxygen anesthesia. A transverse incision was made through the vaginal mucosa at the junction of the cervix and posterior vaginal walls, exposing the subperitoneal areolar tissue. Three nodules were found in this zone. They lay in the muscle coat of the supravaginal cervix, but their external surfaces projected into the areolar tissues inferior to the cul-de-sac peritoneum. They varied from 1 to $2\frac{1}{2}$ cm. in diameter and were firm, lobular, and fixed. Removal was difficult and required excision of a zone of contiguous cervical muscle. Five gold-screened radon seeds of 1 millicurie each were inserted into the bed of the nodules. The vaginal mucosa was approximated after a narrow iodoform gauze drain was left in situ for screening purposes.

The pathologic report of the excised nodules was as follows: "The specimen consists of three firm ovoid tissue masses varying from 1 to 2½ cm. in diameter. They are surrounded by loose areolar tissue. On section they are gray white, largely fibrous. Small areas present a granular appearance. Microscopically, all nodules are similar and present a matrix of connective tissue and occasional involuntary muscle fibers. The matrix supports bizarre proliferating glands (Fig. 6). The majority shows papillary configuration. The broad stromal core is lined by a solitary layer of low columnar or flattened epithelium (Fig. 7). The individual cell is small in size. The cytoplasm is scant. Cilia are lacking. The nucleus which is round or oval in form is small in size, vesicular, and contains fine chromatin granules. The nutrient capillaries are small. In other areas the matrix contains simple gland spaces lined by flattened epithelial cells as noted in the papillary zone. Secretory activity is lacking. Diagnosis: papillary adenoma of cervix, histogenesis uncertain." Since intestinal and uterine struc-



Fig. 7.— $\times 120$. True adenoma of Gärtner's duct. The finer structure of a papillary process is shown. The lining epithelium consists of a solitary layer of flattened or low cuboidal epithelium with a poorly defined membrane and scant pale cytoplasm. The nucleus is vesicular and almost fills the cell body. The stromal core is comprised of fibroblasts.

tures were not reproduced, a diagnosis of "Gärtner's duct adenoma" was made by exclusion. This opinion was confirmed by Dr. James Ewing who kindly reviewed the slides. The occurrence of the tumor nodules beneath the level of the cul-de-sac peritoneum and their intimate association with the cervix certainly supported this viewpoint.

The postoperative course was uneventful, but examination upon discharge showed induration in the posterior and right lateral walls of the cervix. The vaginal wound was healed except for granulation tissue at the site of the drain. When seen Feb. 7, 1934, the patient was free from subjective complaints. Recto-vaginal examination showed a persistent but slight induration on the posterior and right lateral walls of the cervix. The uterus retained its retroverted position. The adnexa were negative. On March 13, 1935, the patient was symptom free, but the nodules were evidently recurring on the right posterior lateral aspect of the supravaginal cervix. In November, 1937, examination showed progressive

spread of the lesion. The right posterior aspect of the portio and supravaginal cervix was shotty and nodular. Biopsy and further radiation were refused. Examination in April, 1939, showed further spread of the nodules which now involved the entire posterior aspect of the cervix. Additional treatment was refused.

SUMMARY

Gärtner's duct represents the persisting distal segment of the mesonephric or Wolffian duct. In the adult female it is rarely retained in toto. Segments are most frequently found in the supravaginal cervix. In specimens of cervix obtained by amputation, rests are uncommon. One instance was observed in 1,413 cases. The microscopic appearance is distinctive. Rests produce no symptoms or pathologic changes and are accidentally discovered. Adenomatoid hyperplasia may similarly be only a laboratory finding. Two cases are herein recorded. A case of papillary adenoma of Gärtner's duct origin has been observed. The symptoms, physical findings and pathologic features are noted. A five-year observation period reveals slow but progressive spread of the lesion.

My sincere thanks are herewith expressed to Drs. Alfred C. Beck, William A. Jewett, and Leo S. Schwartz for permission to include their cases.

1530 PRESIDENT STREET

REFERENCES

- (1) Meyer, Robert: Virchows Arch. **174**: 270, 1903. (2) *Idem*: Ztschr. f. Geburtsh. u. Gynäk. **59**: 233, 1907. (3) Rockstroh, H.: Ibid. **112**: 95, 1935. (4) Rust, W.: Arch. f. Gynäk. **162**: 350, 1936. (5) Sakuraoka, J.: Mith. ü. allg. Path. u. path. Anat. **9**: 179, 1937. (6) Veit, J.: Handbuch für Gynäkologie, Veit-Stoeckel **1**: p. 433, 1930. (7) Wagner, G. A.: Zentralbl. f. Gynäk. **53**: 1336, 1929.

MESONEPHROMA OF THE OVARY

HOWARD W. JONES, M.D., AND G. EMORY SEEGAR, M.D., BALTIMORE, MD.
(From the Surgical Pathological Laboratory of the Church Home and Infirmary and the Johns Hopkins Hospital.)

A SATISFACTORY classification of ovarian tumors has not yet been established, although much has been accomplished recently by correlating the clinical and pathologic features of these neoplasms. In reviewing over 350 true neoplasms of the ovary, a group of 6 has been separated on the basis of their pathologic characteristics. Schiller has recently described a similar group of cases and believes them to be derived from mesonephric tissue. It is the purpose of this paper to describe the clinical and pathologic characteristics of these tumors and to discuss their histogenesis.

CLINICAL CHARACTERISTICS

There are no symptoms which distinguish these tumors from other ovarian neoplasms. All 6 cases occurred after the age of 40. A mass in the abdomen or abdominal enlargement was a frequent complaint. Abdominal discomfort was sometimes noted.

Abnormal uterine bleeding, which is an important aid in classifying ovarian tumors, was usually absent in these cases. In one case there had been slight

irregularity in the periods for about one year, but in this case there were myomas. In an additional case there was uterine bleeding for one week in a patient several years past the menopause, but here the tumor was highly malignant with extensive pelvic involvement and extension into the uterine cavity probably occurred. The absence of abnormal uterine bleeding is in keeping with Schiller's findings.

PATHOLOGY

The tumor may be practically solid, with numerous irregular fluid-filled spaces or may be cystic with papillary projections. Grossly, the latter form is indistinguishable from the common Müllerian papillary cystadenoma. In the present series, 4 are of the solid and 2 of the cystic variety. The largest tumor in the group measured 25 cm. in diameter and the smallest 12 cm. in its greatest diameter. In 4 of the tumors the external surface was smooth, but in 2 the capsule was penetrated by growth. The solid tumors can readily be distinguished from the cystic, but the microscopic similarity of the cells suggests a similar origin.

The solid tumors are composed of microscopic cysts or tubules lined by an endothelial like cell (Fig. 1). These cells are characterized by sparse cytoplasm and projecting nuclei (Fig. 2), and closely resemble those of the mesonephric glomerulus (Fig. 3). In some areas flattening may be carried to an extreme degree, so that the cells bear a striking resemblance to the endothelial cells of the blood vascular system (Fig. 4). There is a tendency for the tubular spaces to be bridged or filled by a growth of lining cells (Fig. 5). Schiller has commented on this as an attempt at glomerular formation, thus supporting the theory of nephritic origin. It is true that the tiny projections may contain capillary loops, but the resemblance to glomeruli is certainly not striking. In still other areas, the tubular characteristics may be lost, and the tumor cells spread out in an irregular manner through the connective tissue framework (Fig. 6).

The connective tissue may be abundant and is characterized by collagenous fibers with relatively few spindle-shaped cells. In other areas the connective tissue may be very sparse, so that the basement membranes of adjoining tubules are in apposition. Hyalinization is a striking characteristic, giving some areas an almost cartilaginous appearance (Fig. 4).

The cystic tumors reflect their papillary tendency in the microscopic architecture. There may be multiple, branching, connective tissue stalks lined by the characteristic endothelial-like cells with bulging nuclei (Fig. 7). The projecting nucleus and the relatively sparse cytoplasm are distinguishing characteristics of the tumor cell.

MALIGNANCY

Of the 6 patients, 2 died of recurrence in about six months. Both of these were of the solid variety. Each of the remaining patients is well at 2, 9, 9, and 14 years following operation. In the 2 fatal cases, the gross appearance of the tumor strongly suggested malignancy, for in each instance the capsule was penetrated by tumor cells. The tumors in the remaining cases were well encapsulated.

HISTOGENESIS

For purposes of classification, the histogenesis of these tumors is of interest. For the following reasons, Schiller believes them to be derived from mesonephric rests which have become included in the ovary.

1. The tumor cells resemble the endothelial cells of glomeruli (Fig. 3).
2. The tumors contain isolated structural units which resemble glomeruli. These mesonephric glomerularlike structures are thought to be mesonephric because they contain only a few capillary loops. The mesonephric glomerulus contains but a few loops and is embryologically more closely related to the ovary than either the pronephros or the metanephros (Fig. 8).
3. Tubules are found in the tumors. These might correspond to the tubules of the mesonephros.

4. These tumors may also occur at the site normally occupied by the mesonephric remains; namely, the broad ligament. One example of this site of origin is included in Schiller's paper.

The Cohnheim theory concerning the role of embryonic "cell rest" tumor development has been greatly narrowed in its application in recent years. However, there is a striking resemblance between the cells of the ovarian tumors

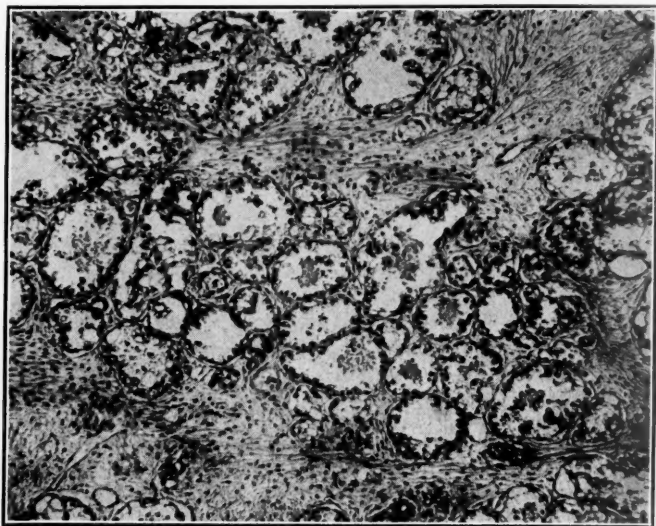


Fig. 1.—Case 1. A low power view of a solid mesonephroma, showing the characteristic small cysts and tubules lined by an endotheliallike cell with projecting nuclei.

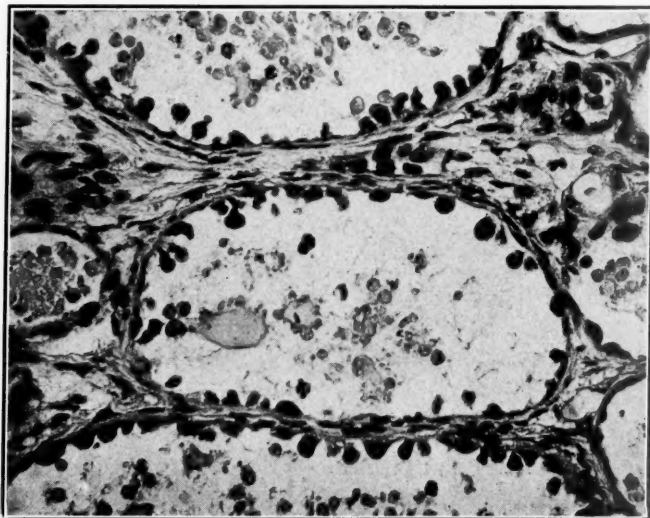


Fig. 2.—Case 2. This is a solid mesonephroma, showing the characteristic flat-lining cell with projecting nucleus.

under discussion and the cells of the mesonephric glomerulus (Fig. 3). On the other hand, it has been most difficult to identify structural units in the tumor tissue which might be taken for distorted glomeruli. As mentioned above, the tumor cells show a tendency to grow into the lumina of the tubules or cysts, but, in our opinion, there is no true resemblance to glomeruli. It is true that the papillary projections of the tumors contain capillaries, but one would expect to find this in any papillary neoplastic growth. However, there are numerous



Fig. 3.—A mesonephric glomerulus. A coronal section through a 14.5 mm. human embryo. These cells are considered by Schiller to be the cells of origin for the tumors under discussion. He has therefore called them mesonephroma. $\times 600$.

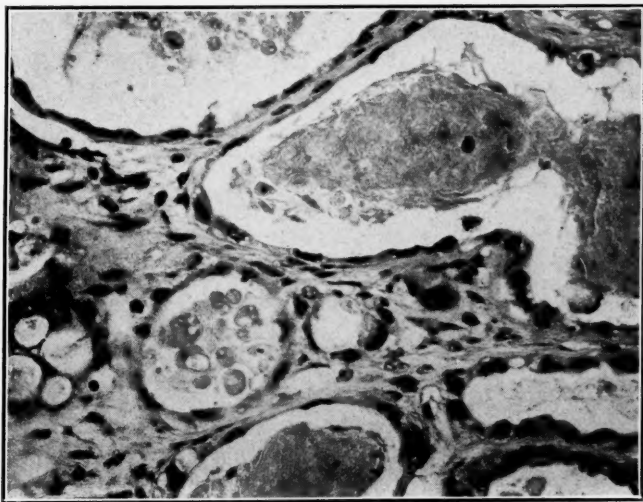


Fig. 4.—Case 2. A high power view of a solid mesonephroma, showing the flattening of the tumor cells that may sometimes occur. These resemble the endothelial cells of the lymph or blood vascular system.

tubular structures which might represent mesonephric tubules. On the other hand, there is nothing about these tubules to indicate a mesonephric origin. In the present series, all tumors have apparently arisen in the ovarian tissue, so that we have not had the opportunity to study a case which has arisen in the broad ligament.

There is one other point which might indicate the embryonic, but not necessarily the mesonephric origin for these tumors. According to Popoff, at certain embryologic periods, the right ovary is found to be less differentiated than the

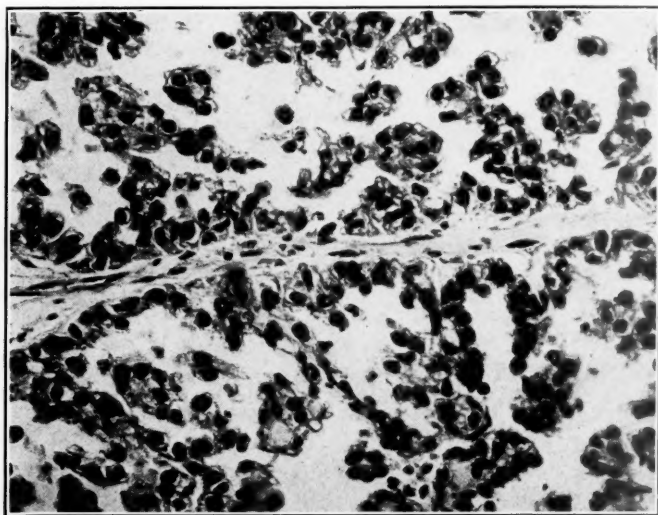


Fig. 5.—Case 4. A high power view of a solid mesonephroma showing the tendency of the cells to bridge the tubular space. In other areas the tubules were completely filled with tumor cells. This patient is well, but only two years have elapsed since operation.

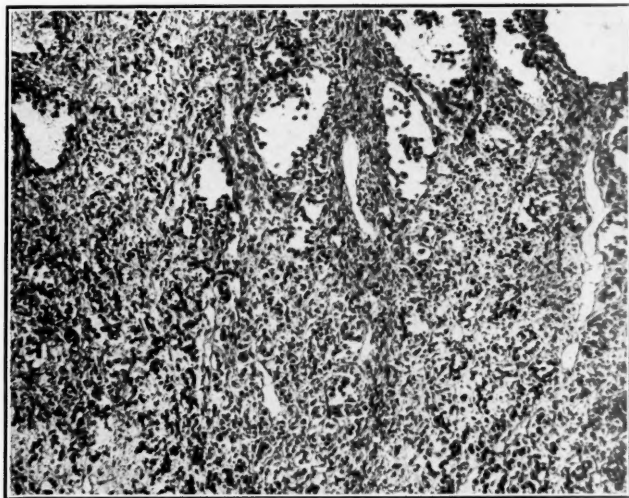


Fig. 6.—Case 3. A low power view of a solid mesonephroma, showing the tumor cells scattered irregularly through the supporting stroma. In the upper portion of this section may be seen the characteristic cystic structure with flat cells and projecting nuclei.

left, and in birds the right ovary is present only in a rudimentary form. Therefore, one might expect the right ovary to contain more embryonic remnants. If this were so, there should be more tumors arising from the right than from the left side. Such is the case. In the 6 cases herein reported only 1 was present solely in the left ovary, and in Schiller's series there was but 1 out of 10 cases similarly located. Seegar has also found that other tumors thought to arise from embryonic rests, for example dysgerminoma, are much more commonly found in the right ovary. However, this evidence is no more than suggestive.

The theory of the mesonephric origin of these tumors while plausible is not yet proved.

SUMMARY

From a series of 350 ovarian neoplasms, 6 cases have been described with distinguishing pathologic features. The tumors occurred after the age of 40 and presented no characteristic clinical features. Two were found to be malignant and 4 were benign. The mesonephric origin of these tumors has been discussed.

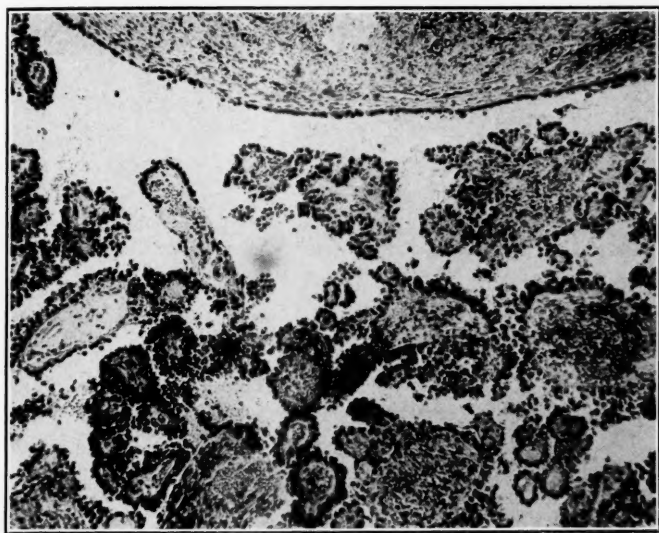


Fig. 7.—Case 5. A low power view of a cystic mesonephroma. Grossly this tumor could not be distinguished from a common ovarian papillary cystadenoma. However, its lining cells indicate that it should be classified as a mesonephroma. This patient is well fourteen years after operation.

CASE HISTORIES

CASE 1.—(C. H. I. Path. 8710.) A 63-year-old woman was admitted to the hospital for the removal of a mature cataract. During the routine examination a mass was felt in the lower abdomen and operation was advised. Menopause was several years previously and there had been no bleeding since. At operation March 19, 1928, a mass extending almost to the umbilicus was freed from the bowel. A right salpingo-oophorectomy was performed.

The specimen measured 13 by 10 by 7 cm. and retained the shape of the ovary. The fimbriated end of the attached tube was closed, but otherwise appeared normal. The surface of the ovary showed a nodular appearance with variegated colors of red and yellow. In several places the capsule had been penetrated and a squatty cauliflower growth protruded. The cut surface of the tumor showed a yellow partially necrotic center with islands of opaque gray and small patches of hemorrhage.

Microscopically, this tumor was composed of small tubules, and in the illustration the cells show a tendency to overgrowth (Fig. 1).

Patient died of recurrence within six months.

CASE 2.—(C. H. I. Path. 10676.) A 41-year-old woman had noticed a mass in the lower abdomen for about two months. For the past year there had been slight irregularity of the menstrual periods. Seven years previously she had had a bilateral salpingectomy. On March 6, 1930, a supravaginal hysterectomy and right oophorectomy were performed. The left ovary appeared normal and was not removed.

The uterus measured 6 by 5 by 4 cm. There were intramural myomas measuring up to 3 cm. in diameter. The right ovarian mass measured 15 by 12 by 8 cm. Section through the mass showed the entire tumor filled with a soft edematous very cellular tissue of yellowish color. The microscopic appearance is seen in Figs. 2 and 4.

Patient is living and well nine years after operation.

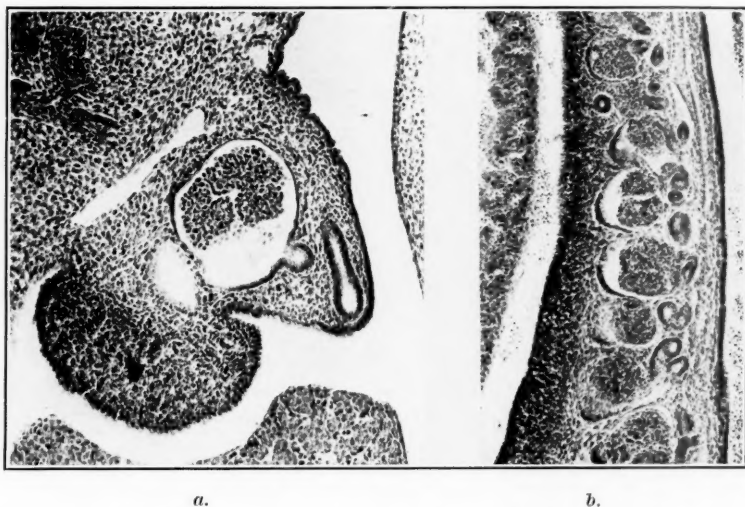


Fig. 8.—(a) This is a coronal section through a 14.6 mm. human embryo. This shows the proximity of the mesonephros to the genital ridge and indicates the possibility for mesonephric cells to become mingled with the cells of the developing gonad. $\times 150$. (b) A sagittal section through a 12.0 mm. human embryo again illustrating the proximity of the mesonephros to the genital ridge.

CASE 3.—(C. H. I. Path. 19787.) A 58-year-old woman complained of diarrhea of two months' duration. Two months ago she had slight vaginal bleeding for one week. There had been no recurrence of this. For the past month she had had some lower abdominal pain. There was a hard mass in the lower abdomen extending to the umbilicus. On May 2, 1938, the left tube and ovary and the right ovary were removed. There was extensive pelvic involvement and nodules were felt in the liver. A small nodule was removed from the peritoneum.

The right ovarian specimen measured 12 by 10 by 8 cm. The surface was smooth. The attached tube appeared normal. The mass was soft and edematous and on section showed irregular cystic spaces containing clear uncoagulated fluid. The left ovary measured 4 by 2 by $1\frac{1}{2}$ cm. It has a cellular appearance and showed some papillary nodules with a structure similar to that seen in the large mass from the opposite side. The microscopic appearance is shown in Fig. 6.

Patient died within six months of recurrence.

CASE 4.—(C. H. I. Path. 19112.) A 72-year-old woman entered the hospital complaining of a mass in the lower abdomen. She had noticed this for about four months. Normal menopause twenty-two years before. There had been no bleeding

since. At operation on Oct. 14, 1937, large bilateral masses were shelled from the pelvis. The uterus was grossly normal and was not removed.

The left ovarian mass measured 16 by 14 by 10 cm. The capsule was well preserved. A normal appearing tube was thinned out over the surface. Section through the mass showed it to be solid cellular tissue with numerous cysts. The cysts were filled with a cloudy fluid. The right ovarian mass measured 11 by 7 by 5 cm. Its appearance was similar to that of the opposite side (Fig. 5).

Patient living and well two years after operation.

CASE 5.—(C. H. I. Path. 5748.) A 54-year-old woman entered the hospital complaining of lower abdominal discomfort and enlarging abdomen of three months' duration. She had a normal menopause eight years before. There had been no bleeding since. At operation April 9, 1925, a large cyst arising from the right ovary was found to fill practically the entire abdomen. This was tapped and removed by clamping the pedicle. The uterus contained a small myoma and was removed.

The excised cyst measured 25 cm. in the collapsed state. It was unilocular and the inner wall was studied with a cauliflower growth. The growth did not extend through the wall at any point. The microscopic picture was typical of the cystic form of mesonephroma (Fig. 7).

Patient is living and well fourteen years after operation.

CASE 6.—(C. H. I. Path. 11391.) A 45-year-old woman was admitted to the hospital because of a mass in the lower abdomen. She had lost 30 pounds in weight during the past six months. A normal menopause occurred 3 years ago. There had been no postmenopausal bleeding. At operation on Nov. 17, 1930, a large cyst of the right ovary was ruptured in delivery. A panhysterectomy and bilateral salpingo-oophorectomy were performed.

The ovarian cyst was thin walled and the inner lining was covered with numerous small papillary projections. There was one solid central portion. The uterus and other tube and ovary were normal.

The patient is living and well nine years after operation.

REFERENCES

- Popoff, N. W.: Arch. Path. 9: 31, 1930. Schiller, W.: Am. J. Cancer 35: 1, 1939. Seegar, G. E.: Arch. Surg. 37: 697, 1938.

VAGINAL USE OF ALUMINUM HYDROXIDE AND COLLOIDAL KAOLIN

S. P. SAVITZ, M.D., L. J. GOLUB, M.D., AND H. A. SHELANSKI, M.A.,
PHILADELPHIA, PA.

(From the Department of Zoology, University of Pennsylvania, Philadelphia General Hospital, and Department of Gynecology, Temple University Hospital)

THE need for a nontoxic, nonirritating vaginal cleanser has long been recognized. The preparations which are employed for this purpose are in most instances objectionable either because of corrosive nature, toxicity, irritating properties or general ineffectiveness. A suitable substance for this use should have none of the above properties and yet have the ability to remove the cervical and vaginal debris present in the vaginal tract. Aluminum hydroxide and colloidal kaolin* have been used previously, as an application on cotton sponges, for the purpose of removing from the vaginal tract mucus which tended to obscure lesions present in the

*Aluminum hydroxide gel 80.0 per cent, kaolin 19.0 per cent, sodium benzoate 0.5 per cent, mixed phenols 0.5 per cent (consisting of eucalyptol 1 part, menthol 1½ parts, and thymol 4 parts). Supplied through the courtesy of John Wyeth & Brother, Inc., Philadelphia, Pa.

cervix, fornices, and external os.^{1, 2, 3} Most of the preparations used heretofore for this purpose were not very effective in their action. Since the action of these substances was so effective as a cleanser, and therefore, as an aid to diagnosis, the following study was undertaken to investigate their action and effectiveness when used as a cleanser in the form of a vaginal douche.

When applied to the vaginal walls, cervix, fornices and external os, aluminum hydroxide gel and colloidal kaolin immediately coagulate any mucus or debris with which they come in contact, and this coagulated mass is readily removed by rinsing with water. Complete removal of this masking mucus was found to facilitate diagnosis by increasing visibility of underlying tissue to a degree we have not observed previously with other cleansing agents.

Aluminum hydroxide and colloidal kaolin were compared with other substances which have been used to remove vaginal and cervical debris and mucus. These substances are water, normal saline, hypertonic saline, sodium bicarbonate, tincture of green soap, proteolytic enzymes, silver nitrate, various mercurial antiseptics, 5 per cent solution lysol, and gentian violet. The first four substances have only such mucus removing properties as can be attributed to the mechanical action of flushing and so remove mechanically some of the debris present in the vaginal cavity without acting on the mucus which adheres to the tissues. Tincture of green soap also removes some of the vaginal debris but does not dislodge the mucus on the tissues. It slides over this mucus without affecting it in any way except by the mechanical scrubbing employed in its use. Furthermore, tincture of green soap is quite irritating to tender and eroded vaginal tissue; this irritating action is increased when the vaginal tissues are scrubbed with this substance. The proteolytic enzyme preparations have some action in digesting mucus but their use is rather cumbersome, requires considerable time, and the method of application is such that all portions of the vaginal tract cannot be reached effectively. Silver nitrate, because of its corrosive nature, is not to be recommended in cleansing the vaginal tract. The other antiseptics used vary little from the action of water. The use of an antiseptic on mucous coated vaginal tissue may be ineffective because the antiseptic must first penetrate the mucus in order to reach the tissues. If the antiseptic used does penetrate this mucus, its action may be so changed as to have very little or no effect upon the tissues. Aluminum hydroxide has none of the objectional qualities of the above mentioned substances, and to date has been used satisfactorily in over four hundred patients, as an aid to diagnosis by removal of vaginal and cervical mucus and debris, and in 120 cases as a simple cleansing vaginal douche.

TABLE I

CONDITION	NO. OF CASES	TIMES PER WEEK	NO. OF WEEKS	RINSING
Nonspecific leucorrhea	21	4	3	Morning
Leucorrhea due to mild cervicitis	14	7	4	Morning
Leucorrhea due to moderate or marked exocervicitis	8	7	4	Morning
or endocervicitis	11	7	4	Morning
Pretherapeutically in trichomonas vaginitis	12	4	1	Morning
Pretherapeutically in moniliasis	5	4	1	Morning
Salpingitis (with hot water), 2 oz. to 2 qt.	6	3	Indefinitely	Morning
Chiefly as a measure in vaginal cleanliness	43	3	Indefinitely	Morning or immediately

This mucus-coagulating effect of aluminum hydroxide and colloidal kaolin may be strikingly demonstrated *in vitro* by adding it to a 5 per cent solution of gastric mucin or to mucus removed from the body.

The above described action also takes place when the preparation is used as a vaginal douche. The patient is instructed to use one-half ounce of the aluminum

hydroxide-colloidal kaolin mixture together with eight ounces of water in a hydrostatic bag. After cleansing with this mixture, the patient may rinse immediately with several quarts of warm water. If continued action is desired, the patient should not rinse for several hours after applying the mixture. This douche may be repeated as often as is desired without any harmful effect. The pH of the mixture is about 7.0 and supplies neither acid nor alkali to the vaginal tract. It is a neutral, mucus-coagulating, nontoxic, nonirritating substance. If acidity is desired therapeutically, it may be supplied by agents specifically for this purpose.

RESULTS

Table I shows the types of condition in which this douche has been used. In this study there have been 43 patients who were given the douche chiefly as a measure in vaginal cleanliness, 21 patients in whom the leucorrhea present was due to a nonspecific infection (by nonspecific infection is meant infection due to organisms other than *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, and *Monilia albicans*), 14 cases of leucorrhea due to mild cervicitis, 12 cases of leucorrhea due to *Trichomonas vaginalis*, 11 cases of leucorrhea due either to moderate or marked endocervicitis, 8 cases of leucorrhea due to either moderate or marked exocervicitis, 6 salpingitis cases, and in 5 cases of leucorrhea due to *Monilia albicans*.

This table also gives the details of its use in the various conditions. In the trichomonas and monilia cases, where there is a marked tenderness present, due to either of these infections, and treatment cannot be started immediately, the use of the douche eases the irritation, so that the proper therapeutic measures can be taken. In the salpingitis cases the patient uses two ounces of the mixture to two quarts of hot water every other day for as long as is desired. All of the cases responded to this form of cleansing and showed improvement after its use. In none of the patients in whom the aluminum hydroxide-colloidal kaolin mixture has been used has there been any toxic or untoward reaction.

SUMMARY AND CONCLUSIONS

1. The aluminum hydroxide-colloidal kaolin mixture has proved to be a valuable aid in establishing diagnosis of vaginal pathology and is an effective vaginal cleanser in the form of a douche.
2. It has been used successfully as a general vaginal cleanser, in cases of leucorrhea due to nonspecific infection, mild cervicitis, moderate and marked exocervicitis and endocervicitis, in cases of trichomonas vaginitis and monilia vaginitis as a pretherapeutic measure, and in cases of salpingitis.
3. The aluminum hydroxide-colloidal kaolin mixture may be used as often and as long as desired without any harmful effects.

REFERENCES

- (1) Golub, L. J., and Shelanski, H. A.: J. Lab. & Clin. Med. 22: 1155, 1937.
- (2) Shelanski, H. A., and Savitz, S. P.: AM. J. OBST. & GYNEC. 37: 294, 1939.
- (3) Shelanski, H. A., and Kern, F. M.: Ibid. 37: 161, 1939.

338 SOUTH TWENTY-FIRST STREET

Knoll, W.: Do Athletes Have Difficult Labors? Med. Klin. 35: 845, 1939.

From a study of 73 married female athletes, the author concludes that individuals who participate in athletics do not have more difficult labors than women not interested in sports. A large proportion of the athletes who had children, took up their sport activities again soon after each labor. Likewise the author denies that women athletes are more often sterile than other women. Hence, young girls may safely indulge in all forms of athletic activities.

THE USE OF TESTOSTERONE PROPIONATE IN THE TREATMENT OF THE MENOPAUSAL PATIENT

WITH A PRELIMINARY REPORT ON THE USE OF PELLETS OF
CRYSTALLINE TESTOSTERONE PROPIONATE

D. SILBERMAN, M.D., F.A.C.S., H. M. RADMAN, B.S., M.D., AND
A. R. ABARBANEL, A.B., M.D., BALTIMORE, MD.

(From the Department of Gynecology, Surgical Division, Sinai Hospital)

THIS report presents our experiences with the use of the so-called "male" sex hormone, testosterone propionate, in the treatment of the menopausal patient. The menopausal syndrome may occur during or after the transition period, at which reproductive function ceases. This phenomenon is a normal physiologic one, characteristic of the process of aging. The precipitating factor appears to be the withdrawal of estrogens, resulting from ovarian failure to respond to the pituitary gonadotropic hormone. Therefore, estrogenic substances have been administered for the relief of this syndrome. Estrogens, however, are not specific in this respect as other hormones, including progesterone (1), testosterone (2) and desoxyeorticosterone (3) may act similarly.

The therapeutic rationale for the use of testosterone propionate has been fully reviewed elsewhere.⁴ Suffice to say, testosterone is not only a powerful androgen but also a very potent gynecogen.

MATERIAL AND METHODS

In the past year, fifteen menopausal patients, including two surgical castrates, have been treated with testosterone propionate. Their ages varied from 39 to 50 years. Because the degree of severity of symptoms depends a great deal upon the constitutional status of the patient, as well as upon environmental factors and intercurrent diseases, each case was carefully studied and only those diagnosed as having severe menopausal symptoms were accepted for treatment. Social service workers were called in when necessary to complete evaluation of the case. Appropriate sedation and whatever other medication was deemed necessary were prescribed, where needed.

DOSAGE

The individual dosage used consisted of 5 mg. of testosterone propionate per cubic centimeter of sesame oil. Injections were given subcutaneously, usually in the deltoid region, sufficiently deep to cause no swelling in the overlying skin. At first, the hormone was given two to three times a week. With clinical improvement the injections were repeated at weekly, and then bi-weekly intervals. Therapy was maintained for four to six weeks after symptoms had disappeared.

Two additional methods of administration have been utilized. When the patient's symptoms were well controlled by subcutaneous injections of the hormone, tablets containing 5 or 10 mg. of testosterone propionate, combined with an enteric coated bile salt preparation, were prescribed for oral use. The other method consisted of the subcutaneous implantation of pellets of crystalline testosterone propionate; three to four pellets, weighing 6 to 9 mg. each, were embedded under the

skin through a No. 12 needle. The average total weight of the pellets per patient was approximately 25 mg. Although this method of administration was at first used in only those patients who had a recurrence of symptoms after cessation of therapy, it has now become the method of choice in all severe cases since it has yielded the best and most consistent results. Further studies, with the use of pellets only, will be reported in a later communication.

Where arthralgia was also present, estradiol dipropionate was alternated with the testosterone propionate until the joint symptoms disappeared.

The following case histories illustrate the method of approach used in the treatment of our menopausal patients.

CASE 1.—A white, married housewife, aged 48 years, whose menopausal symptoms began in the summer of 1937, appeared at the clinic complaining of severe flushes, followed by cold sweats, both day and night, headaches, blurring of vision and poor appetite. She had previously been treated with estrogenic substances with indifferent success. Physical examination revealed poor condition of her teeth; otherwise she was essentially negative. Pelvic examination was negative.

She was given 5 mg. of testosterone propionate subcutaneously twice a week for three weeks with such marked improvement that the interval between injections was increased to one week. Dental consultation was secured, she was given vitamin-B complex (brewer's yeast) to stimulate her appetite, and barbiturates for sedation. She became symptom free after six weeks and did not return until five weeks later, when she developed a severe upper respiratory infection accompanied by a return of her flushes. Therapy was repeated with the same success. A few weeks later when well regulated with 5 mg. of testosterone propionate once a week subcutaneously her flushes suddenly increased in frequency and severity. Inquiry revealed that many domestic difficulties had arisen at home. With the aid of the social service worker, the situation was adjusted, and her response to therapy once again became gratifying.

Whenever therapy was withdrawn for periods of three to four weeks, her symptoms rapidly reappeared. After one month without therapy, four pellets of crystalline testosterone propionate, totaling 26.1 mg., were implanted subcutaneously. In two weeks her flushes had entirely disappeared and since then (ten weeks) she has remained symptom free. With this form of therapy, she has felt much better than she had with the injections. It is interesting to note that she became tanned over the exposed portions of her skin, an observation previously reported in the male.⁵ This phenomenon was observed in two other cases.

CASE 2.—A white, married housewife, aged 46 years, was referred to the gynecologic dispensary because of severe and frequent hot flushes, sweats, poor appetite, insomnia, urgency and frequency of urination. The past history revealed a story suggestive of gall bladder disease but was otherwise negative. Physical examination, except for moderate obesity, was within normal limits. Pelvic examination was negative. Suction biopsy revealed a slight proliferation of the endometrium. Blood and urine examinations were negative.

She was given 5 mg. of testosterone propionate subcutaneously twice a week. At the same time, a reducing diet was prescribed and barbiturates were given for sedation. With clinical improvement injections were reduced to one a week. Her urinary symptoms rapidly cleared with no special medication. She apparently had a normal menstrual period five weeks after therapy with the hormone had been instituted. (Her last menstrual period had occurred eight months before.) Suction biopsy at this time revealed a hypoplastic endometrium. Injections were continued; flushes, now occurring two to four times a day, were very mild. She developed la grippe four weeks later with a marked aggravation of her symptoms. Dosage had to be increased to 15 mg. (3×5) per week for two weeks in order to control her flushes. After another month, when well regulated, she was given daily oral doses of testosterone propionate, 5 mg., combined with bile salts. She was maintained thus for a week but at this time, proving sensitive to the bile salts, the latter were

omitted. The 5 mg. tablets orally, without the bile salts, proved ineffectual and were discontinued. With the return of symptoms three pellets of crystalline testosterone propionate, totaling 22.2 mg., were implanted subcutaneously. Fifteen days later she experienced a scanty flow of uterine bleeding. She has now remained practically symptom free for two and one-half months, and the pellets are still palpable under the skin of her thigh.

CASE 3.—A forty-year-old, white housewife came to the dispensary complaining of increasingly severe hot flushes, insomnia, formication, poor appetite, and marked nervousness. She had undergone a panhysterectomy two months before. Physical examination, except for a moderate degree of deafness, otosclerotic in origin, was essentially normal. Pelvic examination revealed the absence of the uterus and adnexa.

Therapy consisted of 5 mg. of testosterone propionate twice a week subcutaneously. Relief became apparent in ten days. In three weeks, her flushes were considerably milder and her appetite had greatly improved. In a month, she was able to do her housework without tiring easily. Injections were now given once a week for six more weeks. Her flushes at this time occurred at intervals of two to three days and were very mild in character. She failed to return until one month after her last injection when she complained that her flushes were returning more frequently and with increasing severity. She was given testosterone propionate orally, combined with bile salts, 5 mg. daily for two weeks, then three times a week for three more weeks. Her symptoms were completely relieved and she has since remained practically symptom free (two months).

RESULTS

The vasomotor phenomena, hot flushes, cold sweats, acroparesthesias, etc., were practically completely relieved in every case. The elapsed time before a satisfactory response was obvious, varied from ten days to three weeks. Remarkable, indeed, was the very early disappearance of lassitude, tiredness, easy fatigability and the rapid return to normal physical vigor. Concomitantly, the appetite improved as well as the general sense of well being.

Two patients with genitourinary complaints of urgency, urinary frequency, mild burning and nocturia, for which no pathologic basis could be ascertained, became practically asymptomatic during the treatment.

Three patients became tanned over the exposed areas of their body during the winter months.

Two cases with menopausal arthralgia received relief from their vasomotor phenomena but showed no improvement of joint symptoms until estradiol dipropionate was used alternately with the testosterone propionate.

The uterine bleeding that was apparently provoked in the second case, and which has been noted in two other cases in which pellets were implanted, remains inexplicable in the light of our present knowledge.

Although carefully watched for, no signs of masculinization of any sort whatsoever were noted. No effects upon libido were observed.

DISCUSSION

The therapeutic value of testosterone propionate in the relief of the vasomotor phenomena associated with the menopause seems clearly established from both the results obtained in this series and those reported by others.^{2, 6} The *modus operandi* by which these symptoms are ameliorated is as yet obscure.

The route and method of administration play an important role in determining the total dosage necessary to secure clinical relief. When the hormone is given by injection, the subcutaneous route is preferable to the intramuscular one, as the subcutaneous route provides for a longer duration of action and thus is more effective per given dose.⁷ When testosterone propionate is given orally, the effectiveness is so

enhanced by the simultaneous administration of bile salts,⁸ that this method of therapy is discontinued if the bile salts are not well tolerated by the patient.

From our preliminary studies with the subcutaneous implantation of pellets of crystalline testosterone propionate, it is felt that this procedure will eventually supplant the other methods of administration of the hormone except possibly in mild cases. It has yielded by far the smoothest and most consistent results and from the patients' point of view will prove the most economical one.

SUMMARY AND CONCLUSIONS

Fifteen menopausal patients, including two surgical castrates, suffering from severe menopausal symptoms, were treated with testosterone propionate. In every case, the vasomotor phenomena, hot flushes, sweats, paresthesias, etc., were practically completely relieved. In addition, there was observed a rapid return to normal physical vigor along with an improvement in appetite and the general sense of well being. Genitourinary complaints of mild urgency and urinary frequency disappeared spontaneously during therapy. Three patients developed a peculiar tanning over the exposed portions of their body. In two patients with arthralgia in addition to the usual menopausal symptoms, estradiol dipropionate was alternated with testosterone propionate with complete relief.

The individual dose given by injection was 5 mg. of testosterone propionate. Injections were given subcutaneously two to three times a week and the interval lengthened with clinical improvement. With control of symptoms, oral therapy was instituted. This consisted of the daily administration of 5 to 10 mg. of testosterone propionate combined with bile salts.

The most satisfactory method of administration, from all viewpoints, has been the subcutaneous implantation of pellets of crystalline testosterone propionate totaling approximately 25 mg.

The testosterone propionate used in this study was supplied by the Ciba Pharmaceutical Products, Inc., under the trade name of "Perandren—Ciba."

The authors acknowledge their indebtedness for the preparation of the pellets to Dr. Gerson Biskind, of the Department of Pathology, Johns Hopkins University.

REFERENCES

- (1) Laroche, G., Simonnet, H., and Bompard, E.: *Compt. rend. Soc. de Biol.* 126: 1159, 1937. (2) Salmon, U. J.: *Proc. Soc. Exper. Biol. & Med.* 37: 488, 1937. (3) Salmon, U. J.: *Proc. Soc. Exper. Biol. & Med.* 41: 515, 1939. (4) Abarbanel, A. R.: *AM. J. OBST. & GYNEC.* (In press.) (5) Hamilton, J. B.: *Science* 88: 481, 1938. (6) Laroche, G., Simonnet, H., and Bompard, E.: *Compt. rend. Soc. de Biol.* 129: 953, 1938. (7) Deanesly, R., and Parkes, A. S.: *Proc. Roy. Soc., London, s. B.* 24: 279, 1938. (8) Abarbanel, A. R.: Unpublished data.

INTERNAL ENDOMETRIOSIS (ADENOMYOSIS) OF THE URINARY BLADDER

MARTIN L. DREYFUSS, M.D.,* NEW YORK, N. Y.

(From the Department of Laboratories of Beth Israel Hospital)

STARR JUDD, in 1921, described the first case of endometriosis of the bladder. Ottow, in 1927, succeeded in making the first correct preoperative diagnosis by cystoscopy. In the same year, Plaut made the diagnosis in the operating room and confirmed it by rapid frozen section. Since that time, the number of cases reported has increased slowly but steadily. After v. Mikulicz' survey in 1936, further cases have been described by Perlmann (1934), Weijtlandt (1934), Erle (1935), Chauvin (1936), Mark (1937), Adams, Stoeckel, Homma (1938), and Reynolds (1939).

The clinical picture of endometriosis of the bladder is well defined today. The same cannot be said for its histogenesis and pathogenesis. The case which I am reporting offers, in my opinion, several interesting features which may help to clarify some mooted points, particularly concerning histogenesis.

CASE.†—C. B., a 26-year-old female, was admitted to Beth Israel Hospital with a diagnosis of acute cystitis on Oct. 26, 1938. (Admission No. 106153.) Her chief complaint was suprapubic pain on urination.

Menstrual history: $14 \times 3.7 \times 23$. The patient had considerable dysmenorrhea, two days before and on the first day of menstruation. She had never missed a period. The flow was moderate. The patient was unmarried and had never been pregnant.

One and one-half years ago the patient was operated upon at another hospital. At that time a simple ovarian cyst was removed together with one tube and the vermiform appendix. There were no unusual findings.

Three days before admission, simultaneously with the onset of her menses, the patient noticed a sharp suprapubic pain and burning on urination. There was also an increase in frequency. No pain in back, no fever, no gross hematuria were noticed. These symptoms had been occurring off and on for the past year, their onset coinciding with that of the menses although they often lasted longer than the menstrual period.

Vaginally, a firm tumor on the right side of the uterus was felt anteriorly. Otherwise the clinical examination was negative.

Urine.—(Catheter specimen.) Specific gravity 1024, acid, bloody, albumin 1-plus, white blood count 8-10 per high power field, a few squamous epithelial cells. **Blood Count.**—3.89 million red blood cells, 8,000 white blood cells. Slight anisocytosis.

Intravenous Urography.—There was a large filling defect in the basal portion of the right side of the bladder. The filling defect was also seen in the cystogram.

Cystoscopy.—There was a bulging tumor on the right side extending from the sphincter margin backward to the posterior wall. The mucosa was not ulcerated. The tumor was the size of a quarter coin.

Biopsy.—Inflamed bladder mucosa with large epithelial nests of Brunn.

Preoperative Diagnosis.—Neoplasm. The pathologist (Dr. A. Plaut) on the basis of the history and cystoscopic findings, mentioned the possibility of an endometriosis of the bladder.

Operation.—(Dr. S. Wilhelm.) The peritoneum was opened, no implants were found. The bladder was opened and the tumor excised. It was round, elastic and situated in the right lateral wall, extending from the sphincter margin backwards

*Dora Paul Cancer Research Fellow.

†Thanks are due Dr. E. A. Horowitz for permission to use the clinical data.

to about 1.5 cm. from the right ureteral orifice. It was covered by a thickened mucosa. The trigone was normal.

Gross Specimen.—Ellipsoid specimen 3.5 by 3.5 by 2.5. Part of the surface appeared charred. On the surface a square of 3 cm. was formed by deep red bladder mucosa in which three dark brownish red spots, about 6 mm. in diameter, were situated. On bisecting, thin brownish fluid, suggestive of altered blood, came out. The cut surface looked grayish, with streaked markings. There were, notably near the periphery, a few small indistinct cavities from which the fluid exuded.

Microscopic Description.—The tumor was bisected at right angle to the bladder surface, one slice 1 mm. thick cut in serial sections, the rest at levels. Every tenth slide was stained. The stains used were hematoxylin-eosin, v. Gieson, elastica and mucicarmine.

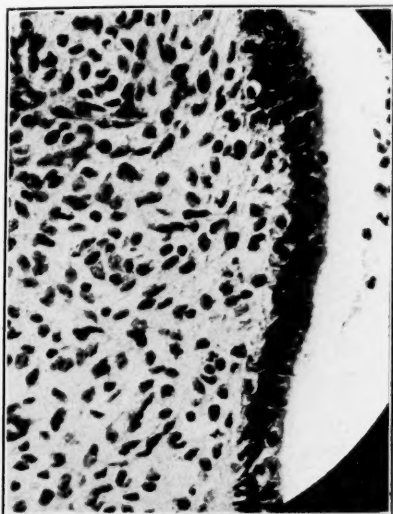


Fig. 1.



Fig. 2.

Figs. 1 to 4.—The photomicrographs represent small portions of the endometrioid structures within the bladder wall.

Fig. 1.—The stroma has the characteristics of cytogenic tissue. The epithelium is cylindrical.

Fig. 2.—The stratified epithelium of the bladder surface is continuous with the single layered cylindrical epithelium of the gland. The aspect of the stroma is somewhat altered by edema.

The bladder epithelium extended with deep folds into the submucous layer. It was somewhat thickened. Many nests of Brunn were seen. Some of them, when followed in serial sections, appeared separated entirely from the surface epithelium. Others were continuous with it and represented the deepest parts of the folds. They were in part solid with occasional intraepithelial vacuoles, in part they had a lumen and were somewhat glandlike with their inner epithelial layer formed by cylindrical cells. The mucin reaction in these cells was negative. No secretion was found in the lumina. Some of them communicated with the lumen of the bladder, others had no demonstrable opening.

The submucous layer was highly edematous and inflamed. In one area the surface epithelium was entirely missing (site of biopsy).

The muscle coat was thick, but otherwise not remarkable. There was no evidence of new formation of muscle. The edema and inflammation extended into the internal muscle layer. In the subserosa occasional inconspicuous accumulations of lymphocytes were seen. The serosal cells were poorly preserved.

The most important findings were numerous glandular structures which occupied the submucosa and branched toward the muscle coat. They were present also in the muscle, more in the internal than in the external layers. Nowhere did they reach the subserosa. They were lined by a single layer of columnar, partly ciliated, epithelium. The epithelium rested on a basement membrane. Some of the glandular structures were cystic. The epithelium of these cystic glands was flat or cuboidal, in some places cylindrical. The lumen often contained well-preserved, or degenerated erythrocytes, cellular detritus, and amorphous matter. In a few, large accumulations of polymorphonuclear leucocytes were present. Some of the larger glands had papillary protrusions. Only traces of cytogenic tissue could be found around the glandular structures in the submucosa, while it was more abundant around the glands in the muscle coat. Brownish, granular pigment was situated near the glands, both between and within connective tissue cells. There was no new formation of muscle, nor was the fibrous tissue increased.



Fig. 3.

Fig. 3.—The transitional epithelium of the bladder mucosa is continuous with characteristic mucinous epithelium.

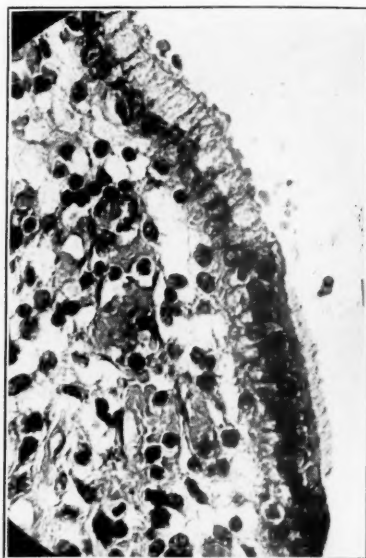


Fig. 4.

Fig. 4.—Ciliated epithelium and mucinous epithelium touching each other in one of the endometrioid glands.

In one area, in the center of the lesion, the surface epithelium reached particularly far into the submucosa, forming thus deep crypts, and the nests of Brunn were numerous and large. Here the glands opened into the crypts or into the cystic nests. The transitional surface epithelium was continuous with the columnar epithelium of the glands. The transition between the two types was rather sudden. In one ramification, the transitional epithelium changed into characteristic mucous epithelium which gave a positive intracellular mucicarmain stain. In another ramification, near the muscle coat and away from the surface, the continuity of the cylindrical epithelium was interrupted by the presence of of mucous epithelium for a short distance.

Diagnosis.—Internal endometriosis of the urinary bladder.

COMMENT

R. Meyer has distinguished three types of endometriosis of the bladder:

1. Internal, originating probably from bladder epithelium.

2. External, originating from serosal cells.
3. Collision, resulting from the combination of 1 and 2.

It is evident from the literature that most of the cases belong to Group 2. Regardless of the mechanism involved, whether there be implantation (Sampson), penetration (Haselhorst), or metaplasia, all these cases have one principal characteristic in common: the bladder is invaded from without by the endometrioid structures. Therefore, these cases must be considered as external endometriosis of the bladder.

Regarding internal endometriosis of the bladder (Group 1), the various authors are not in accord as to the criteria for establishing such an entity. Erle lists 21 cases out of 30 as "primary," Weijtlandt 3 out of 35. According to Stoeckel there are no cases of true internal endometriosis of the bladder at all. Mark expresses himself in similar fashion. Adams considers as "primary" only those cases in which there is no continuity with the sex organ and no peritoneal involvement, and in which previous operations have not caused a trauma to the bladder. The fact that, in many cases of "primary" endometriosis, the process starts evidently from without detracts from the usefulness of this term. It is much more accurate to continue the distinction of external and internal endometriosis. The latter term then would include those cases in which the origin can be traced to the bladder epithelium. It must, however, be kept in mind that the endometrioid structures may penetrate up to the bladder epithelium in cases of external endometriosis as well. The direction in which the glands ramify may then be helpful for a correct interpretation.

It seems surprising at first that endometrioid structures should arise in the bladder epithelium. Some authors as Erle, Oehlecker, Mueller and Frommolt thought that undifferentiated coelomic cells, or some other dysontogenetic rests in the bladder, gave rise to the endometriosis. The bladder, in fact, in the embryo, is lined originally by a single layer of cylindrical epithelium. This epithelium assumes its definite appearance only in embryos of 55 to 60 mm. length. On the other hand, the presence of glands in the normal bladder is not generally admitted. Outside the trigone where sometimes aberrant urethral glands may be found, glandular structures are not considered a normal finding, although Moellendorf, Lendorf, and others have described rudimentary glands in the bladder.

It is well known, however, that the bladder epithelium may form glands under pathologic conditions. The transformation of the epithelial nests of Brunn into glands has been shown recently by Patch and Rhea (cystitis glandularis). Nests of Brunn and gland formation are usually but not exclusively found in the inflamed bladder (Putschar).

Another proof for the potentialities inherent to the bladder epithelium is the formation of mucous epithelium. It has been found in chronic cystitis and particularly in exstrophy of bladder. Mucus-producing adenocarcinoma of the bladder has also been observed occasionally (Hueckel). Homma, Mueller, and Frommolt described mucous epithelium in their cases of endometriosis of the bladder. According to Homma, it is due to a metaplasia of the bladder epithelium. Mueller and Frommolt considered it as evidence of a dysontogenetic origin and thought that it was derived from aberrant rests of the primary gut.

True internal endometriosis of the bladder is rare. Only the cases of Mueller (1927, Case 1), Frommolt (1929, Case 1), Oehlecker (1930) can be considered as true internal endometriosis of the bladder. A probable case of internal endometriosis is that of Erle. There is no microscopic description but the illustration is highly suggestive.

In other cases (Weijtlandt and Reynolds) no biopsy was taken and therefore no conclusive judgment is possible. It is only by microscopic evidence that we can decide whether we are dealing with internal or external endometriosis.

Pathogenesis: It is evident from the cyclic character of symptoms and the cyclic change in size and appearance which can be observed with the cystoscope, that these structures are under hormonal and especially under ovarian influence. Phillips described different functional pictures in two subsequent biopsies. R. Meyer,

in one case, observed decidual reaction in the endometrial structures. In most cases, however, the only anatomic sign which could be referred to cyclic change is the presence of old and fresh blood.

Particularly impressive are the clinical observations of Mueller who was able to follow by serial cystoscopic examinations, the effect of pregnancy, x-ray, and hormone treatment upon the endometriosis.

These facts are definitely in favor of a dependence upon hormonal stimuli which most probably are ovarian. But there is no evidence, whatsoever, that endometriosis is caused by the action of hormones. Endometriosis might very well originate in an entirely different way and still come under hormonal influence secondarily. One cannot ignore the fact that, in many cases, the onset apparently follows mechanical trauma as operation, childbirth, curettage or some inflammatory condition in the pelvis or in the abdomen. In the case described by Plaut, a simple appendectomy only had been performed. It is difficult to imagine that this may have caused a hormonal imbalance. Even less conceivable, in such a case, is an implantation of endometrium.

For the cases of internal endometriosis of the urinary bladder, I would rather think that mechanical or inflammatory stimuli cause multipotent cells of the bladder epithelium to differentiate and that perhaps the direction in which they develop is influenced by hormones.

SUMMARY

The origin of the endometrial structures from the bladder epithelium is demonstrated in a case of internal endometriosis of the bladder.

The causative role of ovarian hormones in the genesis of endometriosis of the bladder is unproved. Once established, however, endometriosis is functionally connected with the ovary.

REFERENCES

- Adams, P. S.*: J. Urol. **40**: 390, 1938. *Chauvin, M.*: Bull. soc. franç. d'urolog., p. 318, 1936. *Erle, H.*: J. A. M. A. **104**: 1401, 1935. *Homma, K.*: Zentralbl. f. Gynäk. **62**: 2115, 1938. *Hueckel, R.*: In Henke Lubarsch, Handbuch d. path. Anat. **6**: 2, 1934. *Lendorf, A.*: Anat. Anz. **17**: 55, 1901. *Mark, E. G.*: J. Urol. **37**: 799, 1937. *Mickulicz-Radecki, F. v.*: Zentralbl. f. Gynäk. **60**: 2530, 1936. *Patch, F. S., and Rhea, L. J.*: Canad. M. A. J. **33**: 597, 1935. *Perlmann, S.*: Urol. & Cutan. Rev. **38**: 76, 1934. *Phillips, R. B.*: J. Obst. & Gynaec. Brit. Emp. **41**: 165, 1934. *Plaut, A.*: Zentralbl. f. Gynäk. **53**: 3358, 1929. *Putschar, W.*: In Henke Lubarsch, Handbuch d. path. Anat. **6**: Part 2, 333, 1934. *Reynolds, L. R.*: J. Urol. **41**: 157, 1939. *Stoeckel, W.*: Gynaekol. Urologie in Stoeckel's Handbuch der Gynaekologie **10**: Part 1, 1938. *Weijlandt, J. A.*: Proc. Roy. Soc. Med. **19**: 15, 1934.

Synephias: Spinal Anesthesia With Percaine for Cesarean Section, Bull. Sec. d'obst. et de gynéc. **28**: 137, 1939.

In the Strasbourg Maternity, 67 cesarean sections were performed under spinal anesthesia. No serious complications were observed. This anesthetic was employed in spite of its well-known dangers because it preserves satisfactory uterine contractility, diminishes bleeding during operation, prevents postoperative atony, and is harmless to the child.

Local anesthesia is excellent, but it takes much more time and proves painful in women who suffer violent uterine contractions. Furthermore, local anesthesia is difficult to carry out when performing a cervical cesarean section with exteriorization of the uterus.

J. P. GREENHILL.

COMBINED EXTRA- AND INTRAUTERINE PREGNANCY*

DAVID B. LUDWIG, M.D., PITTSBURGH, PA.

THE co-existence of intra- and extrauterine pregnancy is comparatively rare and sufficiently interesting to have been the subject of some excellent reviews by observers in this and other countries.

Combined pregnancy is to be distinguished from compound pregnancy, as in the former the intra- and extrauterine pregnancy occurs simultaneously, and in compound pregnancy the intrauterine pregnancy is superimposed on a previously existing ectopic pregnancy which has terminated in lithopedion formation.

Bland¹ in 1933 quoted authors who had collected 183 cases of compound pregnancy from 1582 to 1926, summarized 13 cases recorded to 1933, and reported one of his own, making a total of 197 cases. Mathieu¹⁰ reviewed the literature from 1933 to 1937, collected 32 additional cases, including a personal one which totals 229.

There has been considerable variance in the number of cases of combined pregnancy reviewed by equally exacting observers due to difference of opinion as to the authenticity of some cases.

The publication of Gemmel and Murray's⁷ exhaustive study in 1933, summarizes 217 cases from Duverney's case in 1708 to the end of 1931. Mathieu added 19 cases from 1928 to 1931 which he failed to find in the study of Gemmel and Murray. Mathieu's study through 1936 has added 57 cases. These combined with the 217 assembled by Gemmel and Murray make a total of 274 recorded cases to the end of 1936.

Novak¹³ in 1925 reported 32 cases collected from the literature from 1913 to 1925, including 2 cases of his own. These added to the 244 cases assembled by Neugebauer (quoted by Novak¹³) from 1708 to 1913, bring the total to 276, and with 57 cases reviewed by Mathieu, total 333 through 1936.

I have reviewed 17 cases in the recent literature and am reporting 3 original cases which makes a total of 353 cases through 1938.

It is interesting to note that in 20 cases reported all mothers recovered. There were four pregnancies came to term (three intrauterine and one extrauterine) culminating in living children. One intrauterine pregnancy terminated at eight months, another continued through 6.5 months with the probability of having continued to term.

AUTHOR'S CASES

CASE 1.—Mrs. H. I., colored, aged 25, was admitted to the Allegheny General Hospital Dec. 19, 1935. Her last menstrual period began September 30, being seven days late. Slight spotting of blood began November 10 and continued to the present time. On November 25 the patient experienced a severe attack of cramplike pain in both sides of the lower abdomen. This was followed by intermittent attacks of pain culminating in a severe attack on December 18. Her menstrual periods had always been regular. She had one miscarriage five years ago and has a child three years of age.

Physical Examination.—The patient was fairly well developed, rather thin and appeared very ill. Her abdomen was much distended with some rigidity of the left lower abdomen. The blood count showed red blood cells 3,450,000, white blood cells 24,800, hemoglobin 65. The temperature upon admission was 96.6° F., pulse 120, and blood pressure 80/42. Vaginal examination Dec. 19, 1935, revealed a softened and enlarged uterus in a forward position. A soft tumor mass was located posterior and to the left of the cervix. Diagnosis: Ruptured ectopic pregnancy.

Operation was performed Dec. 20, 1935. The left tube and ovary, the ectopic mass, and the blood (over a quart and mostly clotted) were removed. Due to persistent hemorrhage from the fundus of the uterus just beyond the left broad ligament attachment, a supravaginal hysterectomy was done. A blood transfusion of 650 c.c. was administered during the operation and dextrose and saline immediately

*Reported at a regular meeting of the Pittsburgh Obstetrical and Gynecological Society, Pittsburgh, Pa., April 3, 1939.

SUMMARY OF CASES IN RECENT LITERATURE

AUTHOR	YEAR	AGE	GRAVIDA	DURATION OF PREGNANCY		CASE FINDINGS AND REMARKS
				EXTRA-UTERINE	INTRA-UTERINE	
Clarke	1934	27	ii	--	8 weeks	Right tubal pregnancy ruptured. Salpingo-oophorectomy. Patient recovered.
Clarke	1936	29	i	2 mo.	Term	Right tubal pregnancy ruptured. Partial salpingectomy. Patient recovered. Living child.
Neumann	1935	20	i	2 mo.?	2 mo.?	Left tubal pregnancy ruptured. Partial salpingectomy. Patient recovered.
Neumann	1935	34	vii	2.5 mo.	2.5 mo.	Left ovarian pregnancy ruptured. Oophorectomy. Patient recovered.
Neumann	1936	32	i	?	6 mo.	Intrauterine abortion. Left tube and ovary removed. Patient recovered.
Schürger	1935	--	--	2+ mo.	2+ mo.	Left tubal pregnancy ruptured. Salpingectomy. Patient recovered.
Rainey and Shera	1936	37	ii	3 mo.	2.5 mo.	Twin extrauterine pregnancy. Intrauterine pregnancy expelled at 2½ mo. Patient recovered.
Sertā	1937	40	iii	3 mo.	2 mo.	Right tubal pregnancy ruptured. Salpingectomy. Patient recovered.
Huber	1936	31	v	2.5 mo.	2.5 mo.	Ruptured left tubal pregnancy. Hysterectomy and bilateral salpingectomy. Patient recovered.
Bondurant	1937	34	vii	Term	Term	Extrauterine child recovered. Intrauterine child died on fifth day. Patient recovered.
Figueroa	1937	32	i	2 mo.	2 mo.	Ruptured left tubal pregnancy. Salpingectomy. Patient recovered.
Moudrý and Tachezy	1937	22	--	5 weeks	8 mo. Wt., 2,100 gm.	Ruptured left tubal pregnancy. Salpingectomy. Patient recovered. Child hydrocephalus, died 1 hour after birth.
Moudrý and Tachezy	1938	29	ii	2 mo.	2 mo.	Ruptured left tubal pregnancy. Salpingectomy. Intra interrupted artificially. Patient recovered.
Marten and Meyer	1937	26	ii	6 weeks	2 mo.	Ruptured left tubal pregnancy. Salpingectomy. Hysterectomy. Removal of fetus. Patient recovered.

SUMMARY OF CASES IN RECENT LITERATURE—CONT'D

AUTHOR	YEAR	AGE	GRAVIDA	DURATION OF PREGNANCY		CASE FINDINGS AND REMARKS
				EXTRA-UTERINE	INTRA-UTERINE	
Dolan	1937	28	i	2.5 mo.	Term	Ruptured left tubal pregnancy. Salpingo-oophorectomy. Normal child spontaneous. Patient recovered.
Sugasti	1938	27	ii	2+ mo.	3 mo.	Ruptured right tubal pregnancy. Salpingectomy. Intra interrupted artificially. Patient recovered.
Davydov	----	31	i	6 weeks	2.5 mo.	Ruptured right tubal pregnancy. Salpingectomy. Intra interrupted artificially. Patient recovered.
Ludwig	1935	25	ii	6 weeks	3 mo.	Ruptured left tubal pregnancy. Salpingo-oophorectomy. Hysterectomy. Patient recovered.
Ludwig	1935	31	viii	7 weeks	6.5 mo.	Ruptured right tubal pregnancy. Salpingo-oophorectomy. Observed to 6½ mo. pregnancy. Patient recovered.
Ludwig	1938	24	ii	4.5 mo.	2 mo.	Abdominal pregnancy. Right salpingo-oophorectomy. Patient recovered.

after. Convalescence was rather stormy the first seventy-two hours but very satisfactory thereafter. The patient left the hospital fourteen days after operation.

Laboratory Report.—The uterus measured 7 by 6 by 5 cm. and was quite soft. At the opening in the amputated cervix there was bulging of fetal membranes. The sac was filled with amniotic fluid and contained a fetus measuring 6 cm. in length. The left tube contained some placental tissue and a small embryo (12 mm.) inclosed in a large blood clot.

CASE 2.—Mrs. M. B., white, aged 31 years, was admitted to the Columbia Hospital Dec. 25, 1935. Her chief complaint was pain in the entire lower abdomen which began two weeks before admission, occurring intermittently and becoming progressively worse. Her menstrual periods had been regular. She had had 5 full-term pregnancies and 3 miscarriages. There had been no bleeding since her last menstrual period November 3.

Physical Examination.—The patient was well developed, rather obese, weighing 180 pounds. The abdomen was slightly distended with some rigidity of the lower abdomen. The blood count showed red blood cells 4,450,000, white blood cells 9,050, hemoglobin 90. The temperature upon admission was 98.6° F., pulse 90, blood pressure 130/80. *Pelvic examination:* The cervix was softened. There was a soft rounded mass posterior to the cervix which could not be definitely outlined on account of pain and tenderness. Following the administration of morphine, examination revealed an ectopic pregnancy.

At operation December 28 the right tube and ovary, the ectopic mass, and the blood were removed. The uterus was situated well forward, softened, and the size of a 2.5 months' pregnancy. An intrauterine pregnancy was considered. Convalescence was uneventful. The patient left the hospital fifteen days after operation. She was last seen April 30, 1936, at which time the pregnancy had advanced to 6.5 months.

A report of her continued pregnancy and delivery was not secured as she moved from this neighborhood.

Laboratory Report.—Section of blood clot from the lumen of the tube showed fibrin, red blood cells and placental villi with some lymphocytes in the tubal wall.

CASE 3.—Mrs. M. K., white, aged twenty-four years, was admitted to the Allegheny General Hospital Oct. 11, 1938. A few hours before admission she was seized with a severe pain in the lower abdomen and fainted. She experienced referred pain in the upper abdomen and later in the chest and shoulders, more marked in the right shoulder. There was a history of a miscarriage about Aug. 1, 1938. She bled almost every day from August 10 until a few days ago. Aug. 17, 1938, she was seized with a sharp pain in the lower right abdomen and was admitted to a hospital in the vicinity of Pittsburgh, remaining for seven days. The attacks of pain continued, recurred weekly to the present time. She has lost several pounds in weight and has grown progressively weaker. Her menstrual periods have always been irregular. She had a child one year ago and a miscarriage five years ago.

Physical Examination.—The patient was emaciated, pale grayish color, semiconscious. There was a mass which extended to the umbilicus, uniform in outline, filling almost the entire lower abdominal cavity. The contour of the abdomen resembled an intrauterine pregnancy. There was rigidity and marked tenderness of the lower abdomen and much distention of the upper abdomen. No vaginal examination was made. *Diagnosis:* Ruptured ectopic pregnancy with the possibility of an abdominal pregnancy. The blood count showed red blood cells 1,340,000, white blood cells 16,750, hemoglobin 40. The pulse ranged between 120 and 140, scarcely perceptible at times, blood pressure systolic 62, diastolic not determined.

Operation was performed at 1 A.M., October 12. Curettage showed thickened endometrium and placental tissue. Laparotomy revealed an abdominal pregnancy; the fetus was removed and the cord ligated. A portion of the placenta had become detached and was partially necrotic. The entire placental mass was removed. No active bleeding followed. There were over 2 quarts of blood, mostly fluid, in the pelvic and abdominal cavities, this being the greatest amount of blood the author has seen in any patient who has survived.

The fetus and some amniotic fluid were within the sac. The placental mass had been attached to the uterus, cecum, broad ligament, pelvic and abdominal walls, and portions of the small intestine. The abdominal pregnancy had progressed to a little over four months. The uterus was the size of a 2.5 months' pregnancy, very soft, friable, and but partially movable. The patient was given a transfusion of 1100 c.c. of blood during the operation.

On the second day following operation, the patient expelled some tissue from the uterus. Microscopic sections of this tissue showed it to contain decidual tissue and chorionic villi. *Diagnosis:* Infected placental tissue. Her convalescence was quite uneventful after the first twenty-four hours, and she was discharged fourteen days after operation.

REFERENCES

- (1) Bland, P. B., Goldstein, L., and Bolton, W. W.: Surg. Gynec. Obst. 56: 939, 1933. (2) Bondurant, F.: Illinois M. J., 71: 480, 1937. (3) Clarke, F. J.: AM. J. OBST. & GYNEC. 37: 332, 1939. (4) Davydov, G. L.: Sovet. vrach. zhur. 42: 141, 1938. (5) Dolan, E. J.: J. A. M. A. 110: 1438, 1938. (6) Figueroa Casas, P.: Bol. Soc. de cir. de Rosario 5: 161, 1938; also, Rev. méd.-quir. de pat. fem. 12: 1, 1938. (7) Gemmel, A. A., and Murray, H. L.: J. Obst. & Gynaec. Brit. Emp. 40: 67, 1933. (8) Huber, H.: Ztschr. f. Geburtsh. u. Gynäk. 117: 94, 1938. (9) Marten, M. E., and Meyer, L. M.: AM. J. OBST. & GYNEC. 36: 1071, 1938. (10) Mathieu, A.: Ibid. 37: 297, 1939. (11) Moudrý, J., and Tachezy, R.: Českoslov. gynaek. 17: 130, 1938. (12) Neumann, H. O.: Monatschr. f. Geburtsh. u. Gynäk. 104: 265, 1937. (13) Novak, E.: Surg. Gynec. Obst. 43: 26, 1926. (14) Rainey, E. H., and Shera, A. G.: Brit. M. J. 1: 610, 1937. (15) Schürger, S.: Orvosi hetil. 80: 148, 1936. (16) Sertā, S. R.: Rev. de gynéc. e d'obst. 1: 424, 1938. (17) Sugasti, J. A.: Bol. Soc. de cir. de Rosario 5: 168, 1938.

SIMULTANEOUS BILATERAL TUBAL PREGNANCY

REPORT OF CASE

RICHARD TORPIN, M.D., AUGUSTA, GA.

(From the Department of Obstetrics and Gynecology, University of Georgia School of Medicine)

ACCORDING to H. R. Fishback* who has recently reviewed the literature, there are recorded 76 acceptable cases of bilateral simultaneous tubal pregnancy. His criteria include "description of the fetuses or any portion of them found, as well as of placental material." He presents the third case of simultaneous twin pregnancy in one tube and single pregnancy in the other tube.

Bilateral simultaneous tubal pregnancy must be considered to be a form of double ovum twin pregnancy as also pregnancy in the uterus simultaneously with an ectopic pregnancy, so-called heterotopic pregnancy. Of the two conditions this latter is apparently much more frequent since there are more than 300 cases reported.

Case Report.—L. M. W., colored female, 37 years of age, medium constitutional type, entered hospital Sept. 22, 1938. She was married seventeen years to the same husband. She had had 8 children, 7 of whom are living, aged 5 to 16 years. She gave a history of normal menstrual periods on June 1, July 1, and August 1. She began to bleed vaginally in the first week of September. Before she began to bleed she had bearing down pains in each side of lower abdomen simultaneously. The day following the onset of the pain she began to bleed dark blood, scanty, stopping and starting again and this continued until she was operated upon on September 22. The pain, she states, kept her awake for three weeks. She described it as rolling and cramplike and said that it extended up into her chest on both sides. During this time she fainted whenever she tried to stand. She gave a history of nausea and vomiting which began about the same time as the onset of the pain. She stated that urination caused burning and bowel movement increased her pain.

The physical examination revealed a fairly well-nourished, severely dehydrated markedly anemic negress. The abdomen was distended, and there was a shifting dullness, and marked tenderness over both quadrants. No edema of legs or vulva. Pelvic examination revealed a multiparous perineum and a dark bloody vaginal discharge. The uterus was freely mobile and slightly enlarged. There was a fixed and tender mass the size of an orange in the left adnexal region. Right side was free except for a mass the size and mobility of a normal ovary.

A diagnosis of ectopic pregnancy was made and colpotomy operation ordered, which was done immediately.

Laboratory findings previous to operation: White blood count, 11,000; red blood count, 1,500,000; Hg, 30 per cent; no malarial parasites; temperature, 99° F.; pulse, 80; respiration, 26; urine normal except acetone 2+.

Operation was done on Sept. 22, 1938. Under cyclopropane anesthesia a posterior colpotomy was done, merely making a hole in the posterior cul-de-sac where old dark blood was found; the incision was closed with catgut and a laparotomy operation performed with mesial suprapubic incision. The peritoneal cavity contained more than one quart of old, dark, fluid blood and an orange-sized mass was found in the left adnexal region matted together with the left tube, left ovary, and the omentum. The omentum was ligated and cut free. The left tube, left ovary, and the clot were removed en masse. The right tube contained a walnut-sized mass in

*Fishback, H. R.: AM. J. OBST. & GYN. 37: 1035, 1939.

the middle third. The right ovary was small and cystic. The right tube with the mass was removed and the abdominal wound was closed without drainage.

During convalescence she was given by transfusions, a total of 1,150 c.c. of citrated blood. She recovered and left the hospital on the twelfth day, having had normal temperature for five days.

Pathology report by E. Pund. "Bilateral simultaneous tubal pregnancy. Hemorrhagic dissociation of the chorionic sac in ampulla of right tube forming a mass 3 cm. in diameter. The villi are necrotic and the blood is degenerated. Ruptured and hemorrhagic pregnancy of ampulla of left tube forming a hemorrhagic mass 5 centimeters in diameter, with good preservation of the blood and villi. The sac has ruptured through the tube and is now enclosed partly in the omentum. Suppurative inflammation of the fimbriated end of this tube. Small corpus luteum of left ovary."

NONTRAUMATIC, SPONTANEOUS RUPTURE OF UTERUS

L. S. MICHELA, M.D., A. J. BLAKE, M.D., AND D. E. ZUCKERMAN, M.D.
PATERSON, N. J.

(From the Obstetric Service of St. Joseph's Hospital.)

THIS is a presentation of a case of spontaneous rupture of the uterus, occurring between the seventh and eighth months of gestation, of an unusual type. Mrs. May T., white, aged 29 years (gravida iv, para ii), was seen in the Prenatal Clinic of this Hospital on June 2, 1938. Past history included a mastoideectomy at ten years of age and a dilatation with curettage one year ago, following a miscarriage at two months of gestation. The length of her previous labors was not unusual. Her first delivery was assisted with low forceps; the second was entirely spontaneous. Physical examination on June 2, 1938, was essentially negative. The pelvic measurements were normal and prognosis as to labor was good. Urine and blood Wassermann were negative.

The patient was again seen in the clinic on July 2, 1938, and July 9 at which time she stated that during the preceding month she had had a discharge from both ears with associated headache and diplopia.

She did not return to the clinic until Sept. 22, 1938. At this visit nothing unusual was found. Diagnosis of position was right occiput posterior.

Eleven days after that visit (Oct. 3, 1938) she was brought to the maternity ward by automobile. On admission the admitting nurse noticed nothing unusual about the patient's condition; the fetal heart sounds were in the left lower quadrant, rate 140. At 9 P.M. the patient was seen by the interne on service. He obtained a history of onset of abdominal pains at 4 A.M. of the same day. These pains recurred every five to ten minutes throughout the day. However, the patient went about her daily routine, bothered only by occasional vomiting. At 6 P.M. her pains began to increase in severity until finally she decided to come to the hospital, arriving at 8:40 P.M. At no time had she had any sudden, severe or knife-like pain.

On examination the patient appeared rather pale, pulse was 96 and of good quality, respirations 24. Fetal heart sounds could not be heard by the interne at this time, nor could the nurse who had heard them ten minutes previously obtain them again.

The patient appeared fairly comfortable, complained of no acute distress except for some moderate abdominal pain which, however, was now present almost constantly. The entire abdomen was tender to pressure but was perfectly soft. No uterine contractions were felt. The fetal parts could be easily mapped out, position being left occiput anterior. Pelvic examination revealed the cervix to be soft and about 3 cm. dilated. There was no effacement. Membranes were intact: The head was engaged in the pelvis. No vaginal bleeding or discharge was present.

At 10 P.M. (one hour and twenty minutes after admission) the patient suddenly went into shock, the skin and mucous membranes becoming absolutely blanched, pulse rapid, thready and barely perceptible. Her temperature fell to 95° F., and she became markedly dyspneic, restless, and irrational.

Treatment for shock was immediately instituted. Before the onset of active treatment the death of the patient appeared imminent. However, she picked up rapidly following onset of shock therapy. Color was regained to some extent; pulse was slower and stronger; dyspnea lessened and the patient became rational and cooperative again but was still somewhat restless. She stated that she felt very weak, still had constant abdominal pain and a sensation of numbness in her legs.

At about this time, 10:30 P.M., the abdomen was still perfectly soft. Fetal parts were easily and readily palpable, especially at the upper pole of the uterus in the right upper quadrant of the abdomen. Here the fetal parts (feet) seemed to be just beneath the abdominal wall with no interposing uterine wall present. There, however, appeared to be no uterine asymmetry.

A diagnosis of probable uterine rupture was made and laparotomy indicated. Unfortunately, considerable time was lost in attempting to secure a suitable donor compatible with the patient's type of blood. In the meantime, her condition became worse and she died at 1:30 A.M.

Autopsy revealed the following: "The peritoneal cavity is filled with approximately 3 liters of bloody fluid and large blood clots. Lying free in the abdominal cavity there is a fetus surrounded by an intact amniotic sac. The placenta is still attached to the posterior aspect of the sac and is partially extruded into the abdominal cavity. It can be traced distally into the uterus, which is ruptured at the fundus clear across cornu to cornu. The uterus encircles the neck of the fetus, the head in the uterine cavity being well down in the pelvis. The trunk and extremities lie free in the peritoneal cavity. The uterus is soft, flabby and but loosely applied to the neck of the fetus. The body of the uterus is enlarged to about five times normal size, apparently having retracted after rupture. There are no tumors, scars or other defects in the uterine wall."

Anatomic Diagnosis.—Rupture of fundus of uterus with expulsion of the fetus into the abdominal cavity; fatal intraperitoneal hemorrhage; seven and one-half months' pregnancy.

COMMENTS

This case presents the following unusual features:

1. The location of the rupture.
2. The period of gestation between the seventh and eighth months.
3. The absence of any history or physical findings of trauma or other external cause.
4. An adequate pelvis.
5. The unusually strong resistance of the amniotic sac which did not tear at the time of uterine rupture nor during the two vaginal and the frequent abdominal examinations.
6. The resistance of the patient. She was strong enough to go about during the day, come to the hospital in a car, walk into the ward, and then give a history herself of what occurred during the day even though, in all likelihood, her uterus had ruptured some time before admission.

The peculiar characteristics of this case may perhaps be explained on the basis of the autopsy findings, as follows:

1. The uterus apparently had a weakened muscular wall, possibly due to the dilatation and curettage performed about one year before this conception.
2. With the first uterine contractions the weakened section of the fundus probably gave way. The amniotic sac and its contents entered the rent, at once stopping any bleeding by compression—acting as a tampon.
3. The laceration of the uterine wall continued to increase in size. The walls of the uterus slipped down over the amniotic sac and its contents until about 9 P.M. when the laceration reached the point of placental attachment.

Note: The fetal heart was not heard at 9 P.M. after having been heard only ten minutes previously.

4. The tear of the uterine wall continued to extend as the uterus retracted downward over the amniotic sac and its contents. As the fundus passed by the fetal shoulders, release of the compression occurred with resulting hemorrhage into the abdomen, associated with the onset of acute symptoms of shock.

206 CARROLL STREET

IMPROVED INSTRUMENT FOR ENDOMETRIAL BIOPSY*

ADOLPH JACOBY, M.D., F.A.C.S., NEW YORK, N. Y.

(From the Department of Gynecology, New York Post-Graduate Medical School and Hospital, Columbia University)

THE instrument consists of a cannula about $\frac{3}{16}$ of an inch in diameter and about 10 inches in length. The proximal end has attached a standard Luer hub. The distal 1 inch is slightly curved. The distal end is sealed and rounded. About $\frac{1}{4}$ inch from the distal end on the convex aspect of the shaft a sharp tooth is cut. The convex surface of the shaft immediately below this tooth is cut away deeply for a distance of one inch (Fig. 1).

TECHNIQUE

The cervix is exposed with a bivalve speculum. All secretions from the cervix and vagina are wiped away. The cervical canal, portio and vaginal mucosa are painted with tincture of iodine. The sterile biopsy cannula is introduced, with or without previous cervical dilatation, directly into the uterine cavity. A Sana-Lok syringe is attached to the hub. The plunger of the syringe is drawn back creating



Fig. 1.—Endometrial biopsy cannula with Sana-Lok syringe attached.

suction. A device on the plunger maintains this suction automatically. Several aspects of the endometrial cavity are gently curetted without withdrawing the cannula. The continuous suction draws the fragments of tissue into the lumen of the cannula and syringe. Upon withdrawing the cannula a sucking noise is audible when the fenestrum of the instrument emerges from the external os. This demonstrates that the obturation at the cervix has been effective and continuous suction maintained in the uterine cavity. The tissue obtained is placed in a suitable solution for transmission to the laboratory.

The cannula here suggested has several advantages:

1. It is easily introduced.
2. The cutting edge and fenestrum on the convex aspects permit close apposition to the endometrium.
3. Satisfactory specimens are easily obtained without undue pressure.
4. Danger of traumatization or puncture of the uterus is eliminated.

151 WEST 77TH STREET

*Instrument supplied by Research Department, Becton, Dickinson & Co.

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

MATERNAL WELFARE, WHAT ARE ITS FRUITS?*

JAMES KNIGHT QUIGLEY, M.D., F.A.C.S., ROCHESTER, N. Y.

PERHAPS a better title for this presentation might be, "Are the Efforts Expended in Maternal Welfare Work Justified by the Results?" Maternal welfare falls into the domain of preventive medicine, practically all the planned, constructive work has been done within the past twenty years and most of it within the last decade.

The decline in the obstetric death rate in the United States within the last five years has been quite general in extent and appreciable in amount, therefore it should be of interest to attempt a correlation of this improvement with maternal welfare work. To this end, two questionnaires were sent, one to State Departments of Health and the second to State Medical Societies. Both groups cooperated splendidly and the number of replies and the information furnished were very gratifying. Of the 49 questionnaires sent to State Health Departments, 44 were returned either through the Commissioner of Health or the Director of the Department of Maternity and Child Hygiene and 47 out of 49 State Medical Societies. Information was obtained then from one or both sources from 48 of the 49 states. Let us first consider the replies of Health officials.

It was found that every State Department of Health has a Division of Maternal and Child Health and that in at least eight states these special departments have been engaged in constructive work in maternal welfare for twenty years or more and that in at least fourteen states the Health Departments were alive to the necessity for this work before the passage of Federal legislation. Parenthetically, it might be said that in some of these states action was a result of the Sheppard Towner Act of 1921.

The nature and scope of the work of these Departments of Maternal and Child Health can be briefly tabulated as follows: (1) Organizing and conducting prenatal clinics, including case finding. (2) Lay education, emphasizing the necessity for early prenatal care by radio lectures, posters, and moving pictures, prenatal letters for pregnant women, classes in motherhood, and booklets for the expectant mother. (3) Postgraduate courses for physicians; refresher courses. (4) Demonstration delivery services furnishing nursing care. (5) Consultation service. (6) Establishment of small maternity homes in rural areas. (7) Licensure of maternity hospitals and homes. (8) Public Health Nursing services for prenatal and delivery service. (9) Education, licensing, and regulation of midwives, particularly in the Southern States.

Health officials of all the states where State and County Medical Societies had organized committees on maternal welfare agreed that the reduction in maternal mortality was due in a measure to the work of these committees and with two exceptions said that they had had the enthusiastic cooperation of organized medicine through their committees. I wish to quote here from Dr. J. A. Milne, Director, Maternal and Child Health of the Mississippi State Board of Health, "It is only through the approval of Health Department policies by Maternal Welfare Committees of State and County Medical Societies . . . that an effective program in maternal hygiene can be promoted and aimed toward reducing maternal mortality."

*Read at the Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 7 to 9, 1939.

This cooperation has been shown in various ways: In 10 states the Committee on Maternal Welfare and the State Health Department work jointly, acting in an advisory capacity to the projects that are carried on by the departments with the cooperation of the physicians, developing maternal mortality studies in eleven states, and prenatal and postnatal clinics in almost all states. In addition refresher courses of postgraduate study for physicians have been provided where the lecturers have been members of the State Societies and the expenses were usually defrayed by the State Department of Health in 24 states.

Information gleaned from these questionnaires shows that in every state maternal welfare is receiving the attention it deserves from organized health workers. It shows, in the opinion of the Public Health officials of more than half the states, that Organized Medicine through State and County Medical Societies has been a factor in reducing mortality rates and that their continued efforts will result in still greater improvement. It shows that there has been splendid cooperation between Public Health officials and private physicians and that this has been evidenced in joint effort in such ventures as maternal mortality studies, prenatal clinics, postgraduate lectures to physicians, and many other activities.

Replies to the questionnaires addressed to State Medical Societies showed that in 41 states (83 per cent of the total) maternal welfare committees are organized and working. Most of these committees have been formed within the last eight years. A few are older (Connecticut, 1927, Tennessee and Alabama State Societies organized in 1925). Much older is the Committee of the Maryland Society dating back to 1903, while the granddaddy of them all is in Kentucky where the State Medical Society organized a Committee on Maternal Health in 1851, "believe it or not!"

These committees have been advisory to State Health Departments, have engaged in state-wide maternal mortality studies, have given lectures in postgraduate courses in obstetrics to physicians, have been instrumental in regulation of hospitals including requiring consultation in complicated obstetric cases, have circularized the medical profession with literature on better maternal care. In addition, they have carried on lay education by articles for the press, by giving radio talks and lectures before lay groups.

In addition to State Health Departments and State and County Medical Societies, there are, of course, organizations, national in scope, of extreme importance to the maternal welfare cause: The American Committee on Maternal Welfare (1919), an organization made up of representatives of many national and regional Obstetric and Pediatric Societies; The American Public Health Association; and The Federal Children's Bureau of the United States Department of Labor. First, The American Committee has carried on a program "by furthering the practice of safe and sane obstetrics and by stressing the importance of improved antepartum, intrapartum, post-partum, and postnatal care in the interest of the mother and her offspring and the community." It promoted the organization of regional, state and local maternal welfare committees among medical societies from its very inception. It has sponsored the publication of pamphlets on standards of prenatal care, standards of intranatal or delivery care, standards of postnatal care. It sponsored through a special committee the production of an educational film, "The Birth of a Baby," which has been shown as a feature film in about half of the states to probably millions of people. Second, The American College of Surgeons has formulated minimum standards for obstetric departments in hospitals, the fulfillment of which is required of all ACS approved hospitals. Third, The American Hospital Association has required isolation of the obstetric departments in all general hospitals and a competent staff with power to enforce consultation in complicated cases. Fourth, The Maternity Center Association of New York, now national in scope, has for ten years conducted a continuous educational campaign for better care for the parturient. Two hundred thousand people visited its exhibit at the Century of Progress in Chicago, and its display at the New York World's Fair is attracting even more attention. It annually expends eighty-five to ninety thousand dollars in its propaganda work. Fifth, the Welfare cause owes much to a life insurance company and to a

pharmaceutical concern which devoted whole page publicity in many magazines in urging women to report early for obstetric care. Sixth, Public Health Nursing Service. In this field during the year 1938 there were:

Patients admitted to antepartum nursing service	236,324
Field and office visits to and by patients antepartum	671,790
Patients given nursing service at delivery	19,222
Patients admitted to postpartum nursing service	162,782
Nursing visits to patients postpartum	522,406

The American Board of Obstetrics and Gynecology has raised and unified the standards for specialization during the past ten years.

Having marshalled this extensive array of effort, we might now quite properly ask, how much has the maternal death rate declined? What are the causes of the decline? And can this improvement be correlated in general or in certain communities to maternal welfare efforts?

The trend of maternal mortality in the United States is shown by the graph in Fig. 1.

Between 1930 and 1936, there was a decline from 6.7 to 5.7 per 1,000, or 14.9 per cent. Between 1936 and 1938, there was a decline from 5.7 to 4.2 per 1,000, or 24 per cent in two years (estimated). The rate for 1938 is a provisional one and conservative estimate places it lower than this figure. Between 1930 and 1936 there

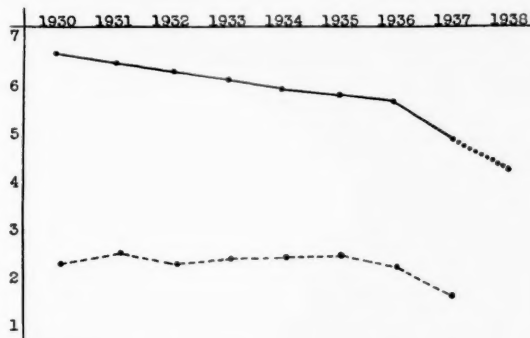


Fig. 1.—Solid line represents deaths per 1,000 births, all causes. Broken line represents deaths from infection, including septic abortion.

was a decline to 57 per 10,000, 14.9 per cent, or 3 per cent per year. From 1936 to 1937, however, the rate dropped to 49 per 10,000, a fall of 14 per cent in one year, almost equalling the total decline of the five previous years, and it is estimated that from 1937 to 1938 there will be at least a 10 per cent decline (with a provisional estimate of 16 per cent), a total of 24 per cent for two years.

If we break down the national maternal mortality figures, we will find that the deaths from toxemia, eclampsia, and allied conditions have not shown a marked drop in the last five years, the greatest gain having been made prior to five years ago. However, a very encouraging finding is that during 1936 and 1937 there was a marked decline in deaths due to infection, including septic abortion.

In the 13 largest cities of the United States the maternal mortality rate has shown a marked recession in the ten years from 1928 to 1937 and in three of these cities, Baltimore, Detroit, and Pittsburgh, the reduction was 50 per cent or better.

States where Maternal Welfare has been established longest and where the work has been very active show the greatest gains. For instance, in New York from 1933 to 1938 the rate fell from 5.4 to 3.6; in Connecticut during the same six years, from 5 to 2.7; in New Jersey from 1931 to 1938, from 5.9 to 3.5 per 1,000; in Pennsylvania from 1935 to 1938, from 5.3 to 3.7, an improvement of approximately 33½ per cent in each state.

What has been the cause of this gratifying lessening of the risk incident to childbirth, the estimated saving of 1,746 lives in 1937 over 1936? One word will pretty well answer this question—education. Public Health work in general is one of education, and this certainly applies to the field of maternal welfare. Education includes better undergraduate teaching in the Medical School; post-graduate education for physicians as given in the refresher courses in Obstetrics; education of hospital authorities to furnish proper institutional care for parturients, separating the obstetric housing and personnel from the other departments in a general hospital, and requiring consultation in complicated cases; educating of midwives, particularly in the southern states where they are still a large factor; and, above all, educating of the public—lay education through literature such as mothers' guides, education through the channels of the Parent-Teachers' Association and other groups, education by radio, by exhibits such as that at the World's Fair, forever stressing the need to report to a physician or clinic early in pregnancy.

An increase in hospital deliveries has accompanied this decline in death rate; the figure for the entire country in 1937 was 45 per cent. We have heard much as to the dangers of births in American hospitals, the greater part of which should be forgotten, for it is not true. I believe that with better regulations of hospitals taking obstetric cases, with the requirement of consultation in complicated cases,

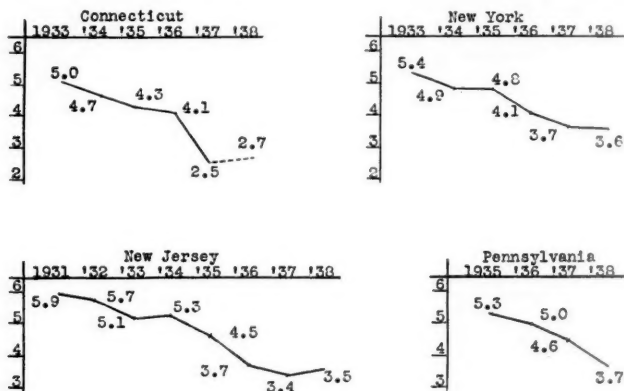


Fig. 2.—Trend of maternal mortality in four states where considerable maternal welfare work has been done.

the hospital is and will be increasingly a factor in lessening the rate. However, the fact that artificial delivery is much easier is probably the worst indictment chargeable to delivery in a hospital. Dr. Colebrook of London, in a lecture on the control of puerperal fever, favors the maternity hospital, for in four years in hospitals only one patient in 700 had hemolytic streptococcus infection, while in domiciliary midwifery the proportion for this period was one to 115. I wish to quote from *An Obstetric Audit* by Scott Runnels, Secretary of the Hospital Obstetric Society of Ohio, "The importance of the hospital as the major factor in the control of maternal mortality is further evidenced by the great increase that has occurred in the hospitalization of the obstetric patient. . . . The percentage of births that occur in hospitals comes closest to indicating the position a locality will have in its maternal mortality standing. One-fourth of the states have more than 60 per cent of their births in hospitals, while the last fourth have less than 25 per cent in hospitals. Comparing the percentage of hospitalization in the various states for 1937 with the maternal mortality rates in the same states for the same year, one makes the striking discovery that twenty-two states fall in the same category on the two charts and that only three states show any marked deviation. The extent of this parallelism in the two charts is the strongest possible argument in establishing the fact that the extent of hospitalization determines the incidence of maternal mortality."

SUGGESTIONS FOR THE FUTURE

First, I wish to quote the conclusions of a paper on Maternal Welfare written by me in 1935. "Let us not become discouraged by the apparent hopelessness of the task. It is formidable, and yet even greater battles in Public Health have been won. Diphtheria, for instance, has been almost eliminated. In the last analysis the author believes that improvement will not be sudden or spectacular but will come only from continued effort, and chiefly in two ways: (1) education of women to seek prenatal care early; (2) in the practice of conservative, sane, clean obstetrics." And now, four years later, we are for the first time noting hopeful signs. This work should not be sporadic or spasmodic, but means continuous effort. Emphasis should be placed upon more refresher courses for doctors with clinical hospital postgraduate courses in hospitals, preferably under the auspices of medical schools; more Analysis (or Maternal Mortality) Committees; more County Committees on Maternal Welfare; lay education as to the dangers of abortion; continued lay education—"If pregnant, see your doctor early"; close cooperation between Public Health officials and Medical Societies in more states.

CONCLUSIONS

1. After remaining stationary for many years, the maternal mortality rate throughout the United States has fallen considerably during the past five years. The American Committee on Maternal Welfare has for twenty years been urging doctors to lead in promoting better maternal care in their localities.

2. For at least ten years much maternal health work has been done by Public Health officials, by Organized Medicine, by Public Health Nurses, and by other agencies.

3. These two facts are not merely coincidental but are closely related.

4. The increasingly large number of deliveries in *approved* hospitals is a factor in a lower death rate.

5. The objectives of a maternal health program should be to reduce not only deaths, but morbidity. Good obstetric care should return a woman to a state of health as good as before her pregnancy, with a living, healthy child. Any plan which reduces mortality will coincidentally reduce morbidity.

6. The battle is not won but only begun. We must continue this work along lines already laid down and expand it.

26 SOUTH GOODMAN STREET

DISCUSSION

DR. FRED L. ADAIR, CHICAGO, ILL.—The campaign for better prenatal care began about 1912 in Boston, in connection with the development of tentative and casual plans for prenatal care. About twenty years ago the American Committee on Maternal Welfare originated in the Society for the Prevention of Infant Mortality. Then we had the Shepard-Towner Act, with a great deal of discussion about mortality rates in this country compared with those in others. This aroused a great deal of antagonism, some contending that our results were as good as could be expected, while others thought they were not.

One of the epoch-making studies was done under the direction of Dr. DeNormandie, which included a study in 13 states for two years and 15 states for one year. This focused attention very sharply on these problems. Then there were the New York City studies under the auspices of the Commonwealth Fund, later the Philadelphia and other studies.

One of the major aims of the American Committee, since it began, was to stimulate the formation of County and State Maternal Welfare Committees in connection with the various state and county medical societies. This has led to the formation of state committees in practically all of the states, but there is still a lot for the state committees to do.

There are a few points that should be emphasized about maternal care. It must be complete and continuous; that is, every community must have facilities for taking proper care of the mothers and their offspring. This includes premarital examina-

tions; also complete prenatal care, adequate facilities for home and institutional care. It will be impossible for many years to come to hospitalize all women who are having babies, even if this were advisable, but certainly hospital facilities should be available for those who need them and for the many cases that cannot be taken care of properly in their homes.

We must have proper post-partum care and every community should have adequate facilities where such care can be continued. The information that is acquired in prenatal care must be used in the delivery and aftercare of the patient. The completeness and continuity with competency of the care are vital factors.

DR. N. F. PAXSON, PHILADELPHIA, PA.—In Philadelphia our own Maternal Welfare Committee, whose findings tend only to confirm what Dr. Quigley has already shown, was started in 1931 under the leadership of Dr. Phillip W. Williams. Our mortality rate has been reduced from 5.6 to 2.8 per thousand for the first six months of 1939, and we believe it can be reduced still further.

When the committee first met there was a wide diversification in methods of handling obstetric abnormalities, but there is now a tendency to pool the knowledge and to accept the best treatment offered. For instance, in septic abortion methods were in vogue which varied from immediate curettage to the most conservative treatment, but there is now a more or less standard method universally agreed upon.

Another point of great value is the formation of a courtesy staff rule which has been adopted by every hospital in Philadelphia. Not alone the obstetricians but also the family physicians have improved their work.

DR. ARTHUR W. BINGHAM, EAST ORANGE, N. J.—In New Jersey the Chairman of the Committee on Maternal Welfare of the Medical Society is also Chief Advisory Obstetrician of the State Department of Health. Each county has a field physician who is a part time man paid by the State Department of Health. He is the contact man between the State and County Maternal Welfare Committees, the State Department of Health and the physicians of the county. His duty is to stimulate among the physicians in his county interest in and familiarity with modern educational and preventive maternal welfare and child health practices.

New Jersey has an advantage in being one of the smaller states with only 21 counties and about 56,000 live births annually. It also has a disadvantage in having a higher percentage of colored births than any other northern state.

DR. ROBERT E. SEIBELS, COLUMBIA, S. C.—The Committee on Maternal Welfare of the South Carolina Medical Association was formed in the spring of 1934 and is the offspring of the series of refresher courses given by Dr. J. R. McCord when he stimulated our interest in the problem. Our efforts have been rewarded by some success, as in the five years there has been a reduction in maternal mortality of nearly 25 per cent. The lowering of the rate has been continuous and has been too widespread to be considered accidental.

With us it is a very different story from that in Philadelphia and New Jersey: for example, only one-half of the deliveries in South Carolina are supervised by physicians, the other being by midwives. We attempt to train the midwife, but about the best we can do is to eliminate the aged and infirm, and the grossly unfit; the best of them are not midwives in a real sense of the word.

About 10 per cent of all the births are in the hospital and of these only 10 per cent are planned hospital deliveries, the others represent admissions of the seriously ill. Maternal Welfare with us is really a rural problem, and to meet it we have instituted a three-point program. Since 1935 we have conducted a survey of each death classed as puerperal by the Board of Health with an annual tabulated report to the State Association.

The hospitals for the most part have open staffs, and there are only a dozen physicians in the state with postgraduate obstetric training. Of the 42 hospitals in the state, we have succeeded in having 10 adopt our rules and regulations for the care of the obstetric patients. The adoption and carrying out of these rules, with the educational efforts directed to the physicians, constitute the two educational features of our program.

Finally a limited program of birth control has been adopted because our surveys have established that 25 per cent of the maternal deaths occur among those who, by reason of previously existing chronic diseases, may be classed as temporarily, or permanently, unfit for pregnancy. There has been set up in each county health department the necessary organization to give contraceptive advice and supplies to those patients who have a prescription requesting it from a licensed physician: for those who have no physician, the county health officer or his clinic physician makes the examination.

DR. IRVING W. POTTER, BUFFALO, N. Y.—In Buffalo, an investigator, partly paid by the County Society has the duty to report the maternal deaths. The committee members study these reports but are not supposed to know what hospital or doctor is involved. We have to contend with many abortions. Deaths from abortion and from ectopic pregnancy are all included as maternal deaths. While this method of reporting is followed the maternal death rate is going to be high. The question of consultation in hospital cases is being considered and at the present time about half the hospitals insist upon consultations.

DR. FREDERICK H. FALLS, CHICAGO, ILL.—I speak in order to enlist your support in the various state medical societies in which you find yourselves, in interesting the members of the society to take this program of maternal welfare seriously. The Illinois State Medical Society had no committee on maternal welfare until this program was started.

It is important also for the universities of the various states to promote this program and to provide postgraduate courses. The refresher courses are not the ideal and nothing but a regular course in an educational institution will really fill the gap. Provision has to be made for the education of the physicians of the state, at very little or no cost to themselves, because the very men who need this work the most are the ones who do not have the funds or do not feel they are able to leave their practice in order to take the course.

DR. R. L. DENORMANDIE, BOSTON, MASS.—In Massachusetts we have been making a five-year study of all maternal deaths and all cesarean operations. We ask if there has been a consultation held before operation, and the answer is usually, yes. But the physician has had a consultation with his best friend. A consults with B, B consults with A. They agree. That is no true consultation such as we think should be held. Furthermore if a consultation is held with a surgeon, he will, of course, do a cesarean for that is the only obstetric operation he knows.

DR. GEORGE F. PENDLETON, KANSAS CITY, MO.—It is interesting that every speaker has dug out the facts in his own community and spoken of the theories applicable to that particular community. Now you and I cannot go home and as doctors in entirely different communities make use of the same plans that are being used in New Jersey or Illinois or some other place. We will have to investigate our own communities and find out where the special trouble is.

DR. R. T. LA VAKE, MINNEAPOLIS, MINN.—Abortion and ectopic are correctly included in computing puerperal morbidity and mortality, in the interests of maternal welfare. One of the most important aims in prenatal care is to bring it about that every woman report to a physician as soon as she suspects pregnancy, that he may impress upon her the danger of induced abortion if she is considering it, that he may give her instructions that will decrease the chance of abortion, and that he may have a chance to diagnose ectopic pregnancy early.

It is my belief that we should get more outstanding results from prenatal care teaching if we would stress, both to the patients and to the physicians, the importance of avoiding contamination of the vagina in the last three months of pregnancy, and establish in the minds of physicians and laity alike a conviction of the greater safety of nonintervention at delivery, except where clearly justifiable indications exist.

DR. J. BAY JACOBS, WASHINGTON, D. C.—Washington has had a very high infant and a relatively high maternal death rate for many years. The average

number of women delivered in our city approaches 13,000 per year. It is estimated that about 9,000 of these are delivered either in private institutions or by private physicians. The remaining 4,000 cases are indigent and receive obstetric care from the Health Department of the District of Columbia. It is interesting to note that during the year 1937 there were registered at our Health Department prenatal clinics less than 700 patients. At the present time the registration has been increased to about 4,000; and so we feel that almost all the indigent maternity cases in the city have been contacted. This of course affords us some control over mortality and morbidity of the indigent population.

DR. JAMES R. McCORD, ATLANTA, GA.—There is probably more in the problem of maternal mortality than good obstetric care. You can take any map of maternal mortality rates and you find that most of the Southern states have high rates. Also, in general, the colored rates are nearly twice as high as the whites. You might immediately say that we are not doing good obstetric work in the South.

I live in a city of approximately one half million people, with a colored population of 150,000. We deliver about 2,200 colored women a year in our clinic in the municipal hospital. Our obstetric service is far from being a finished service but it is a conservative service. Our total operative incidence is 3.96 per cent which includes the packing of the vagina. Our forceps incidence for term and premature deliveries is 1.3 per cent; the cesarean incidence 0.46 per cent, and yet we have an uncorrected maternal mortality rate of 6.4 per 1,000 pregnancies. These women are getting good obstetric care and yet we have a tremendous mortality rate. Approximately 45 per cent of the women on our service are either illegitimately pregnant, the husband unemployed or on W.P.A.

With agriculture in the depths negroes all over the South are moving into the larger communities where they are badly housed and ill fed. Sepsis is the killer of colored women, and certainly on our service we can conscientiously say that it is in large measure not our fault. I do not mean in the least to deprecate good obstetric care, but I do believe that permanent lowering of maternal mortality must be accompanied by a proportionately rising economic level.

DR. QUIGLEY (closing).—Dr. Falls brought up the question of county committees. My feeling is that it is necessary that the larger states should be subdivided into districts of several counties each to facilitate supervision of the work. Committees of the smaller County Medical Societies have little idea as to what is expected of them unless an outlined program can be given them by the State Society Committee. In smaller states subdivision into districts is probably unnecessary.

Replying to Dr. DeNormandie, we have been rather fortunate in Rochester in that all hospitals have agreed to require consultation. The result is that practically all abnormalities, other than low forceps cases, must be seen by a consultant who must be an obstetrician and a staff member of some hospital in the city.

Hoare, E. D.: The Case for Prophylaxis With Sulphanilamide and M. and B. 693, Lancet 1: 76, 1939.

It is possible to protect mice against an infection with hemolytic streptococci by prophylactic treatment with sulfanilamide or the related M. & B. 693. A high bactericidal power was demonstrated in the blood of uninfected human patients treated with sulfanilamide during the puerperium.

The prophylactic use of 1 gm. of sulfanilamide 3 times daily beginning at the onset of labor and continuing for three or four days is suggested. The author would limit its use to circumstances where special risk of infection with the hemolytic streptococcus is present, and he points out the undesirability of routine or indiscriminate use.

CARL P. HUBER.

Society Transactions

AMERICAN ASSOCIATION OF OBSTETRICIANS, GYNECOLOGISTS AND ABDOMINAL SURGEONS

FIFTY-SECOND ANNUAL MEETING

HOT SPRINGS, VA., SEPTEMBER 7, 8 and 9, 1939

The following papers were presented:

Blood Lipids in Pregnancy. Drs. Otto H. Schwarz, S. D. Soule, Bernice Dunie, St. Louis, Mo. (For original article, see page 203.)

Treatment of Hemorrhagic Disease of the Newborn. Dr. W. R. Barney.

Vulvovaginal Mycoses in Pregnancy. Drs. B. Carter, C. P. Jones, R. A. Ross, and W. L. Thomas, Durham, N. C. (For original article, see page 213.)

Tracheloplasty (Sturmdorf Technique) in the Treatment of Sterility. Dr. Oren Moore, Charlotte, N. C. (By invitation.) (For original article, see page 269.)

Stereoroentgenography of 400 Pelves With Clinical Correlation. Dr. John G. Walsh, Providence, R. I. (By invitation.) (For original article, see page 255.)

Hermaphroditism. Drs. Herbert Schmitz and J. P. Greenhill.

Inversion of the Uterus. Dr. Louis E. Phaneuf. (Published in *Surgery, Gynecology and Obstetrics*.)

A Study of Uterine Defense Mechanism. Dr. James R. Goodall.

President's Address. Dr. James E. King, Buffalo, N. Y. (For original article, see page 179.)

Rationale for the Use of Testosterone Propionate in the Immediate Treatment of Excessive Uterine Bleeding. Dr. A. R. Abarbanel, New York, N. Y. (For original article, see page 243.)

Struma Ovarii. Drs. H. M. N. Wynne, James S. McCartney and J. H. McClen-
don, Minneapolis, Minn. (For original article, see page 263.)

The Interrelationship of Surgical Conditions of the Pelvic and Abdominal Viscera. Dr. W. S. Bainbridge. (Published in *J. Internat. Col. Surg.* 2: 417.)

Is There a Clinical Relationship Between Pyelitis of Pregnancy and Pre-eclamptic Toxemia? Drs. R. D. Mussey and S. B. Lovelady, Rochester, Minn. (For original article, see page 236.)

Studies of the Urinary Tract After Delivery. Drs. W. T. McConnell and L. A. Gray, Louisville, Ky. (For original article, see page 227.)

Spontaneous Rupture of the Uterus. Dr. Joseph W. O'Connor.

The Physiology of the Anterior Pituitary and a Note on the Medullotrophic Hormone. Dr. J. B. Collip, Montreal, Canada. (For original article, see page 187.)

Maternal Welfare Work, What Are Its Fruits? Dr. James K. Quigley, Rochester, N. Y. (For original article, see page 349.)

An Electric Timer as An Aid in Counting the Fetal Heart in the Second Stage of Labor and in Spacing and Timing Forceps Traction. Dr. Walter B. Mount, Montclair, N. J. (For original article, see page 272.)

NEW YORK OBSTETRICAL SOCIETY

MEETING OF OCTOBER 10, 1939

The following papers and discussions were presented:

Chemotherapy in Obstetrics and Gynecology. Dr. R. Gordon Douglas. (For original article, see page 275.)

The Pharmacology of Sulfanilamide and Sulfapyridine. Dr. E. K. Marshall, Jr. (By Invitation.)

OBSTETRICAL SOCIETY OF BOSTON

MEETING OF NOVEMBER 21, 1939

The following papers were presented:

Report on the Cesarean Sections Done in Massachusetts in 1938. Dr. Robert L. DeNormandie.

The Estrin Treatment of Dysmenorrhea. Dr. Somers Sturgis.

Correspondence

To the Editor:

I wish to call attention to an error in a footnote of Busby and Fisher's case report, "Tubal Pregnancy Associated with Tuberculous Salpingitis," which appeared in the January, 1940, issue, page 125. In the footnote a recent report of a similar case is attributed to Dr. Arthur Stein; the case report referred to, however, was published by me in the December, 1939, issue, page 1068, and was submitted for publication in May, 1939.

I noted from these reports that my patient was admitted to Michael Reese Hospital, Chicago, on February 16, 1939, Busby and Fisher's patient was admitted to Victoria Hospital on February 17, 1939, and furthermore, Stevenson and Wharton's article on the subject, containing their case report, appeared in the February, 1939, issue of THE AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY. This is indeed an interesting coincidence in point of time.

IRVING F. STEIN, M.D.

Chicago, January 23, 1940.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Abortion

Report by British Abortion Committee, Editorial, Brit. M. J. 1: 1183, 1939.

This article is an editorial comment on the report of the Committee on Abortion, asked by the Home Secretary and Minister of Health to inquire into the prevalence of abortion, the laws relating thereto and recommendations for better enforcement of the laws.

The Committee strongly recommends amendment of the present law so that a medical practitioner who induces abortion to safeguard or restore his patient's health does not render himself liable to prosecution. The Committee implies in its report that it favors legalization of abortion for the relief of conditions that carry a threat to health as well as those that directly threaten life. Because of the possibility of the abuse of such legislation, the Committee recommends control by making consultation prior to abortion obligatory as well as notification of the medical officer of health or other qualified persons. The Committee is not unanimous in its recommendation that such reports of abortion be made available to the police.

The Committee could only make a rough estimate of the frequency of abortion, believing it to be 110,000 to 150,000 per annum, and because of its limitations in arriving at a satisfactory figure, it cannot determine the mortality rate. However, from the evidence available, the Committee concludes that criminal abortion has not become more frequent in recent years but that it is attended by a high degree of risk not only to health but to life.

FRED L. ADAIR AND JOHN NEWDORP.

Grace, W. H.: The Pathological Aspects of Criminal Abortion, Liverpool Med. Chir. J. 45: 136, 1937.

This is a discussion of the legal aspects of abortion from the standpoint of the pathologist. Two types of death are described: (1) a quick death due to shock or, rarely, air embolism and (2) a lingering death due to sepsis. The methods of producing abortion are classified as (1) external violence, (2) administration of drugs, and (3) mechanical injuries to the uterus and its contents by (a) direct violence and (b) injection of fluids. The importance of considering these possible methods at the time of post-mortem examination is emphasized.

CARL P. HUBER.

Keller, R., and Adrian, J.: Molar Degeneration in the Etiology of Early Abortion, Gynec. et obst. 38: 332, 1938.

Histologic examination of early ovular remains revealed Keller and Adrian the great frequency of molar degeneration. They decided to determine whether such molar changes might not be the cause of many unexplained abortions in the early months of pregnancy. Among 305 curettements for incomplete abortions they found fresh villi in only 96 cases. Among the latter cases there were 21 patients with molar degeneration. In 5 patients all the villi had undergone degeneration whereas in 16 cases only part of the villi manifested degenerative changes. Hence 21 specimens among 305 (6.8 per cent) showed molar alterations.

This is in striking contrast to the statement usually made that a mole is found only once in 2,000 or 3,000 pregnancies. The authors are convinced that a molar change is responsible for many abortions in the early months of pregnancy. Since the diagnosis of molar change may be made with the naked eye only in a few cases, histologic study is necessary to prove this point in most cases. Hence, all tissue obtained at miscarriages should be examined microscopically as a routine. This procedure is particularly important in view of the possibility that a chorion epithelioma may follow a hydatid mole.

J. P. GREENHILL.

Young, James: The Habitual Abortion and Stillbirth Syndrome and Late Pregnancy Toxaemia, Brit. M. J. 1: 953, 1937.

Much evidence has accumulated within recent years consistent with the view that an important cause of the habitual abortion-stillbirth syndrome, which has baffled the obstetrician in the past, is a disturbance in the metabolism of pregnancy, in which a deficiency of vitamin E is involved. This evidence challenges the role which vitamin E plays in the prolactin-progesterone mechanism of pregnancy.

The author cites cases showing favorable results in clinical application.

Some evidence is further offered for the view that similar circumstances may supply the missing X factor which was previously described for the nontoxic recurrence of abortion, stillbirth, and accidental hemorrhage in women who are subject to eclampsia and pre-eclampsia. This evidence provides the view that major degrees of deficiency tend towards interruption of pregnancy in the early months without toxemic manifestations, whereas if the deficiency is less marked, the pregnancy is capable of progressing to the later months with a consequent risk of toxemia.

These views raise a question as to the part played by diet in fertility, and more especially as to how far changes in the consumption of essential dietetic elements may have contributed to the declining birth rate.

F. L. ADAIR AND S. A. PEARL.

Currie, David: Vitamin E in the Treatment of Habitual Abortion, Brit. M. J. 2: 1218, 1937.

The author reviews the broadening concepts of general vitamin therapy. He points out work done, showing that vitamin E bears more resemblance to the luteal hormone (progesterin) than to other hormones as regards clinical features, physiologic properties and clinical significance.

Over 50 women were given wheat germ oil during pregnancy, but he includes in his summary only 37 who had aborted more than once. Habitual abortion implies that more than one pregnancy has failed to go to term. Of these 37, who had collectively 130 pregnancies, only 16 viable children resulted. Under treatment these women produced 37 living children. Two of these women aborted; there were 2 sets of twins; and 4 children died in the hospital from prematurity. The appearance of albuminuria of a severe degree was a new problem that arose during treatment. Five patients showed gross signs of toxemia.

He concludes that vitamin E appears to be a definite step forward in the treatment of this most distressing condition of habitual abortion. He advises a dose of 3 minims of the oil extract daily throughout the entire pregnancy, but adds that the dosage and length of time of administering are open to discussion.

F. L. ADAIR AND J. A. HAUGEN.

Kunz, A. C.: Functional Insufficiency of Anterior Pituitary as Cause of Habitual Abortion, Zentralbl. f. Gynäk. 61: 2004, 1937.

In 30 cases of habitual abortion Kunz employed bed rest, corpus luteum extract, and then daily intramuscular injections of prolactin until the end of the fourth month of pregnancy. All of the abortions in these women had occurred

during the second to the fourth month of pregnancy but all were able to carry their pregnancies to full term for the first time under this form of treatment.

It is well known that the corpus luteum hormone favors and protects nidation of an ovum and that estrogenic hormone does the reverse. However, after the second month of pregnancy the corpus luteum is not essential in women. Thus, Ask-Upmark reported 51 cases in which the corpus luteum was extirpated after the second month of pregnancy, and abortion resulted in only one case.

Kunz believes that habitual abortion is due to functional insufficiency of the anterior lobe. In support of this idea is the fact that most abortions occur in the first half of pregnancy, the period during which the greatest demands are made on the pituitary gland. For this reason the author gives prolactin during the first four months of pregnancy to all women who have had abortions.

J. P. GREENHILL.

Rosenfeld, S. S.: Habitual Abortion. Treatment by Injection of Pregnancy Serum, New York State J. Med. 38: 440, 1938.

The author has been treating 20 cases of habitual abortion with about 5 c.c. of normal pregnancy serum injected intramuscularly once a week. Should staining or bleeding occur during the course of pregnancy, the patient is put to bed and doses up to 10 c.c. may be given two or three times a week or even daily, depending on the signs and symptoms. In the absence of bleeding, patients are permitted to pursue their normal routine and duties. The diet is that usually prescribed for a normal pregnant woman, with the addition of cod liver oil and viosterol. Of the 20 patients, 19 gave birth to normal living infants.

J. P. GREENHILL.

Jones, O. Vaughan: The Oestrin Content of Blood and Urine: Its Estimation and Clinical Application, Liverpool Med.-Chir. 45: 112, 1937.

The presence of estrogenic hormone in the blood and urine during the menstrual cycle and during pregnancy is reviewed. An attempt to make quantitative studies of the urine by absorption spectroscopy is described. The results were promising, though in excess of values obtained by biologic and chemical methods. Actual figures are not given.

The value of blood estrin levels in cases where intrauterine death of the fetus has occurred is reported. In 12 cases of suspected missed abortion the blood was negative for estrin and macerated fetuses were subsequently delivered. In 29 cases of suspected fetal death, the blood estrin was negative in 23 with subsequent delivery of macerated fetuses, and in 6 cases the blood estrin was positive with the fetuses later found to be alive. The estrin level in the urine was not altered and the Aschheim-Zondek was not a reliable index.

CARL P. HUBER.

Mondt, W.: The Results of Expectant Treatment of Abortions, Monatschr. f. Geburtsh. u. Gynäk. 106: 291, 1937.

The author reports a series of 365 cases of abortion treated conservatively. He recommends that practitioners employ extremely conservative therapy of abortions. This may entail many visits and immediate activity should hemorrhage occur. Furthermore, the physician will have to be firm in his conviction in spite of the requests of the patient or her family for active treatment. The best place in which to treat abortions is a hospital. The disadvantage of the prolonged period of time necessary to treat abortions conservatively is overcome by the improved subsequent health of the patients.

J. P. GREENHILL.

Cooke, R. G.: An Analysis of 350 Cases of Abortion, Brit. M. J. 1: 1045, 1938.

The author analyzes 350 cases of abortion treated during eight years, 1930 to 1937, and assesses the probable cause of each. It appears that of abortions

admitted to a hospital in an industrial town some 40 per cent are probably procured. The history in such cases is usually freely given, but it is unreliable. The commonest cause in the locality in question is the insertion of slippery elm bark into the cervical canal.

Local interference is usually performed with some mechanical skill, and it is rare to find positive evidence of injury. This indicates that it is more frequently done by someone other than the woman herself. Local sepsis is exceedingly common. Uterine sepsis and pyrexia were present in 35 per cent of the cases, and uterine sepsis without a temperature in a further 10 per cent.

Of the series, 20 per cent of the patients were decidedly ill and 3 per cent died. All the deaths were due to sepsis, except one which resulted from chronic nephritis and uremia. Interesting is one case in which the patient introduced thin slippery elm through the urethra into the bladder. She went to term but was later operated upon for stone of the bladder.

F. L. ADAIR AND S. A. PEARL.

Holtz, F.: The Treatment of Abortion, *Acta obst. et gynec. Scandinav.* 18: 245, 1938.

The author followed up a series of 2,718 abortion cases, some as long as four years. He came to the conclusion that in cases of early abortion without complications and without severe bleeding the interference should be prompt. He is of this opinion because after active therapy there is less frequent spread of infection, a lower mortality, a shorter stay in the hospital and a lower incidence of sterility. When intervention was practiced after a prolonged course, the results were less favorable because there were more infections, more cases of secondary anemia, a longer stay in bed and a higher frequency of sterility.

In late abortions, however, expectant treatment gave better results than active therapy. In most cases both the fetus and the placenta were expelled spontaneously. In cases where the placenta was retained, active treatment was much more satisfactory than conservative therapy.

J. P. GREENHILL.

Hüssy, P.: Abortion and Accidents, *Monatschr. f. Geburtsh. u. Gynäk.* 108: 1, 1938.

In the opinion of Hüssy an abortion rarely is the result of an accident. Even where an abortion follows an accident, the psychic fear plays a greater rôle than the trauma to the body. The world literature offers abundant evidence that even the severest forms of trauma may not interfere with pregnancy because the ovum is very well protected. Gestations are terminated following injuries, chiefly in women who have a tendency to abort. It is very important to rule out all illnesses which may possibly bring about interruption of pregnancy. In order for an abortion to be attributed to an accident it must take place within twenty-four hours of the accident and the physician must rule out any serious illness and predisposition on the part of the patient to abort. Furthermore, criminal attempts to empty the uterus must also be eliminated. Fever is nearly always an indication of mechanical interference.

J. P. GREENHILL.

Petersen, E.: The Use of Spinal Anesthesia for Induced Abortion, *Acta. obst. et gynec. Scandinav.* 17: 449, 1937.

Spinal anesthesia was used by Petersen in 22 cases where an abortion was induced. In all the patients the bleeding was much less than it is when the operation is performed under general anesthesia.

J. P. GREENHILL.

Items

American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting in Atlantic City, N. J. on June 8, 9, 10, and 11, 1940, immediately prior to the annual meeting of the American Medical Association in New York City.

Application for admission to Group A, Part II, examinations must be on file in the Secretary's Office not later than March 15, 1940. Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates. Group A, Part II, candidates will be examined on June 8 and 9, and Group B, Part II, on June 10 and 11, 1940.

The annual dinner of the Board will be held in New York City on Wednesday evening, June 12, 1940, at the Hotel McAlpin.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh, (6) Pa.

Microfilm Sets of Periodicals

The Committee on Scientific Aids to Learning, President Conant of Harvard, chairman, has made a grant to cover the cost of making a microfilm master negative, on the most expensive film, of sets of volumes of scientific and learned journals.

This permits the non-profit Biblofilm Service to supply microfilm copies at the sole positive copy cost, namely 1 cent per page for odd volumes, or a special rate of $\frac{1}{2}$ cent per page for any properly copyable 10 or more consecutive volumes.

The number of pages will be estimated on request to: American Documentation Institute, Science Service, 2101 Constitution Ave., Washington, D. C.

Mississippi Valley Medical Society 1940 Essay Contest

The Mississippi Valley Medical Society offers annually a cash price of \$100, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics) and of practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents of the United States. The winner will be invited to present his contribution before the next annual meeting of the Mississippi Valley Medical Society at Rock Island, Ill., Sept. 25 to 27, 1940. Contributions shall not exceed 5,000 words, be typewritten in English in manuscript form, submitted in five copies, and must be received not later than May 1, 1940. Further details may be secured from Dr. Harold Swanberg, Secretary, 209-224 W. C. U. Building, Quincy, Ill.

Erratum

In the Roster of American Obstetrical and Gynecological Societies, published in the January issue of the JOURNAL, the name of Dr. Ralph A. Reis, of Chicago, was given in error as the President of the Central Association of Obstetricians and Gynecologists. Dr. Reis occupied the office during the previous year. Dr. Jennings C. Litzenberg, of Minneapolis, is the present incumbent.

Books Received

ATLAS OF SURGICAL OPERATIONS. By Elliott C. Cutler, Moseley Professor of Surgery, Harvard University, etc., and Robert Zollinger, Assistant Professor of Surgery, Harvard University, etc. Numerous illustrations on 48 plates (by Mildred B. Coddington), 179 pages. Macmillan Company, New York, 1939.

OBSTETRICAL PRACTICE. By Alfred C. Beck, Professor of Obstetrics and Gynecology, Long Island College of Medicine, Brooklyn, etc. Second edition, 858 pages, 1043 illustrations. Williams and Wilkins Company, Baltimore, 1939.

PICTORIAL MIDWIFERY. By Sir Comyns Berkeley, Chairman of the Central Midwives Board, Consulting Obstetric and Gynaecological Surgeon to the Middlesex Hospital, etc. Third edition, 166 pages. Williams and Wilkins Company, Baltimore, 1939.

PRACTICAL MEDICAL DICTIONARY. By Thomas Lathrop Stedman, M.D., and Stanley Thomas Garber, M.D. Fourteenth, revised edition with etymologic and orthographic rules. Illustrated, 1303 pages. Williams and Wilkins Company, Baltimore, 1939.

OFFICE GYNECOLOGY. By J. P. Greenhill, M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Loyola University Medical School, etc., Chicago, Ill. With 106 illustrations, 406 pages. The Year Book Publishers, Inc., Chicago, Ill., 1939.

THE ART OF ANAESTHESIA. By Paluel J. Flagg, M.D., Visiting Anaesthetist to Manhattan Eye and Ear Hospital, etc., New York. Sixth edition, revised, with 161 illustrations, 491 pages. J. B. Lippincott Co., Philadelphia, 1939.

OBSTETRICIA NORMAL. Professor Raul Briquet, lente catedrático de Clínica Obstétrica e Puericultura Neonatal da Universidade de S. Paulo. With 427 illustrations with 37 in colors. Livraria Editora Freitas Bastos; Rio de Janeiro, 1939.

ANNALES INSTITUTI OBSTETRICI ET GYNECOLOGICI UNIVERSITATIS, Helsingfors. Edidit S. E. Wichmann. Helsinki, Univ. Frauenklinik. Tom. XI. 1935.

CAESAREAN SECTION, Lower Segment Operation. By C. McIntosh Marshall, Honorary Assistant Surgeon, Liverpool Maternity Hospital, etc. With 2 plates and 107 illustrations, 230 pages. Williams and Wilkins Company, Baltimore, 1939.

OBSTETRICAL MANIKIN PRACTICE. By Lyle G. McNeile, Professor of Obstetrics and Gynecology, University of Southern California School of Medicine, etc. With 38 illustrations, 111 pages. Williams and Wilkins Company, Baltimore, 1939.

ENDOGENE ENDOKRINOTHERAPIE IN DER GYNAEKOLOGIE. Von Jules Samuels, Chirurg-Frauenarzt, Amsterdam. A. W. Sijthoff's Uitgeverij-smaatschappij, Leiden, Holland, 1938.

DER ZYKLUS DER FRAU. Reform des Ehelebens. Von Dr. Jules Samuels, Amsterdam. G. Naef, The Hague, 1938.

PRIMER CONGRESO CHILENO Y AMERICANO DE CIRURGIA. Imprenta Universitaria. Santiago de Chile, 1939.

TEXTBOOK OF GYNAECOLOGY. By James Young, Professor of Obstetrics and Gynaecology, University of London, etc. Fifth edition, with 226 illustrations, 425 pages. Adam & Charles Black, Soho Square, London, 1939.

MANUAL OF PUBLIC HEALTH NURSING. Prepared by the National Organization for Public Health Nursing. Third edition, 529 pages. The Macmillan Company, New York, 1939.

JEWISH CONTRIBUTIONS TO MEDICINE IN AMERICA, from Colonial Times to the Present. By Solomon R. Kagan, M.D. Foreword by Professor James J. Walsh. Second edition, revised and enlarged. Illustrated, 792 pages. Boston Medical Publishing Company, Boston, Mass., 1939.

GYNECOLOGIC OPERATIONS and Their Topographic-Anatomic Fundamentals. By Professor Dr. Heinrich Martius, Director of Women's Clinic in Goettingen. Authorized English Translation by W. A. Newman Dorland, M.D. With 404 mostly colored illustrations, 486 pages. S. B. Debour, Publishers, Chicago, 1939.